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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

SEPTEMBER, 1952

ORIGINAL ARTICLES

THE HYDRIODIDE OF DIETHYLAMINOETHYLESTER PENICILLIN-G, NEOPENIL, III: UNUSUALLY HIGH PENICILLIN CONCENTRATIONS IN CEREBROSPINAL FLUID FOLLOWING INTRAMUSCULAR ADMINISTRATION

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PENICILLIN administered parenterally in doses ordinarily used for therapeutic purposes does not readily diffuse into the cerebrospinal fluid[10,11,13]; therefore, intrathecal administration has been widely practiced in the therapy of meningitis. Intrathecal administration does not insure distribution of the antibiotic throughout the spinal fluid and there are frequent neurological complications[5,18] as well as discomfort to the patient. These dangers and disadvantages have prompted investigators to search for more satisfactory methods of attaining therapeutic penicillin concentrations in the spinal fluid. The most frequently reported approach to this problem has been an attempt to increase the blood levels of penicillin by intravenous administration[12,16], by the use of larger doses alone or in conjunction with a renal blocking agent[1].

The relative effectiveness of penicillin in meningitis depends on high concentrations of the antibiotic throughout the central nervous system. For this reason there has been a great deal of interest in the report of Jensen and his associates[8] concerning the hydriodide of diethylaminoethylester penicillin-G which produced unusually high penicillin concentrations in the brain tissue of dogs following parenteral administration. This paper reports a study carried out in an attempt to determine whether this agent pro-

duced higher penicillin concentrations in the spinal fluid of humans than the concentrations obtained with other forms of penicillin.

In this study procaine penicillin was chosen for comparison with Neopenil because they are both depot preparations. The depot effect is much more pronounced, however, with procaine penicillin than it is with Neopenil[7]. N,-N dibenzylethylenediamine penicillin-G is also a penicillin ester and for this reason was chosen for comparison with Neopenil. It is characterized by its very low solubility and its subsequent extremely prolonged blood levels[4]. No studies to determine its tissue concentrations have been reported. Neopenil was compared with potassium penicillin-G since the soluble form is most frequently utilized in the therapy of intracranial infections.

Materials and Methods. The following penicillin preparations were administered intramuscularly in doses of 500,000 units:

Penicillin-G diethylaminoethylester hydriodide (Neopenil•)
Procaine Penicillin-G
Potassium Penicillin-G••
Dibenzylethylenediamine Penicillin-G (Dibenzyl Penicillin•••)

With the exception of potassium penicillin-G, which is soluble, these preparations were administered in aqueous suspension.

Twenty-eight patients attending the Neurosyphilis Clinic at the Philadelphia General Hospital were observed in this study. Between therapeutic courses of penicillin, at intervals determined by the attending neurologist, these patients were subjected to lumbar puncture and venipuncture for diagnostic purposes. Those patients scheduled to have diagnostic studies were given an injection of penicillin (See Table 1.)

One hour after administration of the drug a specimen of spinal fluid was obtained for cell count, protein, serology, and penicillin assay. At the same time a blood specimen for serology and penicillin content was drawn. At a subsequent visit, usually 6 weeks later, the same procedure was carried out, using a different preparation of penicillin. The order in which the different penicillins was given varied from patient to patient. In this manner each patient served as his own control. Specimens of spinal fluid and plasma were frozen and then assayed for their penicillin content by a *Sarcina lutea* cup-plate method[17]. In nearly every case the spinal fluids were grossly clear and colorless. Exceptions to this are shown in Table 1.

Results. The results of this study (Table 1 and Fig. 1) indicate that the spinal fluid concentration of penicillin following a dose of Neopenil is about 10 times greater than the concentrations obtained with equal doses of other types of penicillin. The average blood level obtained with Neopenil was 1.80 U/cc. and the corresponding average spinal fluid concentration was 0.12 U/cc. Procaine penicillin produced an average blood level of 2.11 U/cc. with an average spinal fluid concentration of $<.01$ U/cc. The average plasma level obtained with potassium penicillin was 8.17 U/cc., about four times higher than the plasma level obtained with either procaine penicillin or Neopenil. The average spinal fluid level was .01 U/cc.

Discussion. Increased spinal fluid levels which occur as a result of increased blood penicillin levels have been shown previously[1,12,16]. The present study clearly demonstrates that Neopenil is concentrated in the spinal fluid to a much greater degree than the other types of penicillin compared. Since the plasma levels obtained following Neopenil were equal to those obtained with procaine penicillin and about one-fourth of those obtained with crystalline penicillin, the increased spinal fluid levels must be attributed to a pharmacologic property of the Neopenil rather than to an increased blood-spinal fluid gradient.

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TABLE 1.—COMPARATIVE BLOOD AND SPINAL FLUID LEVELS ONE HOUR FOLLOWING ADMINISTRATION OF 4 PENICILLIN PREPARATIONS TO THE SAME PATIENTS. VALUES IN UNITS/CC.

Pt. No.	*Neopenil*		*Procaine Penicillin-G*		*Potassium Penicillin-G*		*Dibenzyl Penicillin-G*	
	Blood	*CSF*†	*Blood*	*CSF*†	*Blood*	*CSF*†	*Blood*	*CSF*†
1	.82	.05	1.35	< .01	8.4	< .01		
2	.85	.09	2.14	.01	4.22	.13*		
3	1.37	.04	2.43	.01	8.06	< .01		
4	1.23	.32	2.02	< .01	6.20	.01		
5	.71	.03	1.12	< .01	3.71	.01		
6	.75	.02	2.18	.01	9.36	< .01		
7	1.56	.06	1.02	.01	4.53	< .01		
8	4.90	.32	1.55	< .01	10.2	< .01		
9	2.96	.09‡	3.24	< .01	9.8	< .01		
10	2.77	.07	1.94	.01	22.58*	< .01		
11	4.85	.34	4.17	.01‡	7.6	.01		
12	1.68	.08	3.05	.01	7.6	.01		
13	1.26	.20	1.06	.01				
14	.63	.04	1.83	.01				
15	.68	.04	2.73	.01				
16	1.68	.05	3.52	.01				
17	3.00	.22	1.38	.01				
18	1.54	.07	1.21	.01			.33	< .01
19	.25	.12			7.63			
20	2.39	.05			9.20		.10	.01
21	2.38	.16			3.23			
22	2.48	.11			8.00			
23	1.63	.09			10.00			
24	.71	.14			6.82	.01		
25	1.52	.12					.08	.01
26	2.13	.09						
27							.1	.01
28							.14	.01
Av.	1.80	.12	2.11	< .01	8.17	.01	.15	.01

† CSF-Cerebrospinal fluid.

* No explanation for these values can be found. While they are probably errors, they have been included in the average values.

‡ Spinal fluid bloody. Assay done on clear, centrifuged specimen.

The spinal fluid cell counts obtained in this project ranged between 0 and 5 cells per c.mm. We may assume, therefore, that we are dealing with patients having relatively normal meninges.

A great deal of emphasis is now being placed on the blood, serum, or plasma levels obtained with the various antibiotics in the interpretation of sensitivity data for the selection of the proper antibiotic for a given infection. In a general way, the blood levels serve as an index of tissue concentration, but they are rough estimates at best[3].

With the introduction of antibiotics capable of producing high tissue concentrations, it seems more important than ever to consider these tissue concentrations in the interpretation of a sensitivity report in the selection of an antibiotic.

The high tissue concentrations obtained with Neopenil would appear to be related to the physico-chemical properties of this ester. At room temperature the pK value of diethylaminoethylester is 8.54. Therefore about 8.2% of the total ester is present in a non-ionic state[9], while in the ordinary preparations of penicillin, which be-

come highly ionized, the penicillin is an anion. Procaine penicillin and Dibenzyl penicillin depend on hydrolysis of the insoluble material at the site of injection before they will produce blood levels of penicillin; thus the circulating penicillin is in an ionized state as a salt of the plasma cations. To date the ionized forms of penicillin have not shown high selective diffusion into the spinal fluid.

since the conditions of pH and temperature under which biological assays are conducted will completely hydrolyze any intact ester to the active form. Development of an extraction technique to separate the free and esterified penicillin has been undertaken. From the limited amount of data now available it appears that Neopenil is absorbed into the tissues as the intact ester and then undergoes hydrolysis

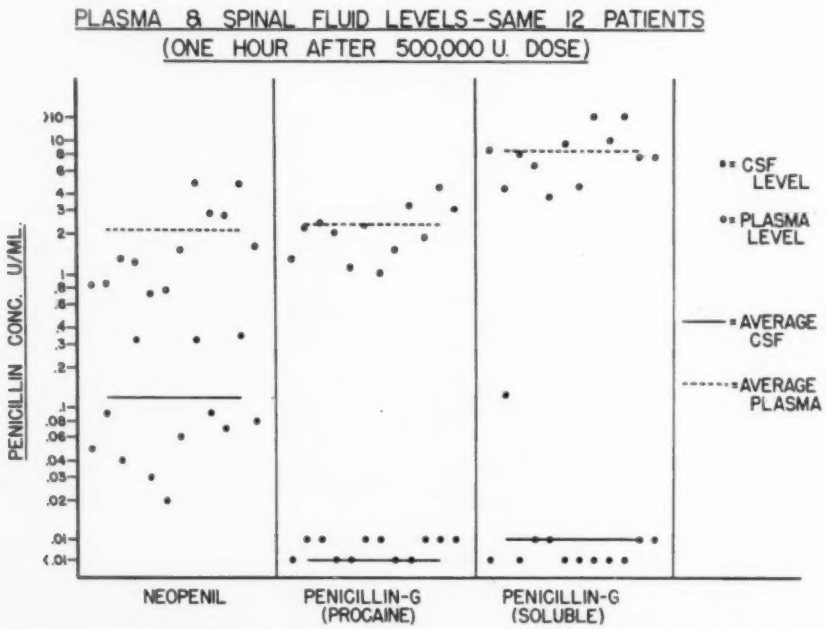

FIG. 1.—Data from 12 patients with neurosyphilis in whom Neopenil, procaine penicillin, and potassium penicillin were compared.

If the penicillin in the spinal fluid is in an esterified form, it is important to the clinician to know whether or not the esterified form has antibacterial activity. Previous investigators[2] working with other penicillin esters have shown that the intact esters have little or no antibacterial activity, but that activity was apparent after hydrolysis. The state of Neopenil activity in spinal fluid has been difficult to determine, to free penicillin[6]. This absorption and secondary release of active penicillin may be considered as a "secondary depot effect." It must be emphasized that the information available at this time is by no means conclusive. In our hands, bacterial pneumonia has responded to Neopenil therapy with the same speed and success as it has to procaine penicillin. This observation would tend to indicate that the peni-

cillin released in the lungs is in an active form. We have not treated either bacterial meningitis or neurosyphilis with Neopenil and therefore have no clinical evidence of its efficacy in these diseases. Further investigations to determine the spinal fluid concentrations with different doses and at varying time intervals are in progress and will be the subject of a future report.

Summary and Conclusions. 1. A study of the relative penicillin concentrations in the spinal fluid produced by procaine penicillin-G, potassium penicillin-G, Dibenzyl penicillin-G, and Neopenil is presented.

2. Neopenil produces spinal fluid levels about 10 times greater than the levels produced by equal doses of other types of penicillin-G in the same patients.

3. The increased spinal fluid levels are thought to be due to a pharmacologic property of the Neopenil, rather than to an increased diffusion gradient.

4. The question of whether or not the penicillin in the spinal fluid is active is raised and discussed.

5. The importance of considering the tissue concentrations produced by an antibiotic is emphasized.

The authors wish to thank the Nursing and Secretarial Staffs of the Neurosyphilis Clinic for their help and cooperation, and Gloria J. Campbell for her technical assistance.

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VITAMIN B_{12} IN THE TREATMENT OF VIRAL HEPATITIS

A Preliminary Report***

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The treatment of viral hepatitis is largely symptomatic with emphasis on bed rest and diet[1,2,4,8,13]. These principles of therapy are especially important in the management of this disease in military personnel who have been debilitated by the rigors of combat. Since there is no chemotherapeutic agent currently available to which the virus of hepatitis is susceptible, it would appear that attempts to hasten the recovery of patients from this disease should be directed at stimulating the processes of hepatic repair.

During the period from July 1, 1950, through July 31, 1951, 2,541 United Nation's military personnel with viral hepatitis were treated at the U. S. Army Hepatitis Center in Japan. An excellent opportunity was afforded for the observance of the various aspects of the disease. The epidemic, *per se*, will be described in other papers by this group.

The present investigation was undertaken to study the effect of the administration of vitamin B_{12} on the course of viral hepatitis. Our interest in this problem was stimulated when one of us (F.W.P.) observed marked improvement in the appetites of anoretic postoperative Korean battle casualties following the intramuscular administration of vitamin B_{12}.

Materials and Method. The data used in this report were collected from 3 groups of 100 patients each. All 3 groups were given a diet consisting of 150 gm. of protein, 350 gm. of carbohydrate and 100 gm. of fat. In addition to the diet, 8 ounces of a high protein milk formula† were given after each meal and at bed time. The total daily intake was 4,000 calories. A check of the patients' trays was made after each meal, and the caloric value of the food which was left was estimated. The patients were given 10% glucose in water by vein or high-protein milk formula in lieu of the food which was not eaten. Bed rest was required of all patients with allowance for one bathroom privilege daily.

Group I received 5 gm. of brewer's yeast 3 times daily and 2 multivitamin tablets‡ 3 times daily in addition to the diet and bed rest. Patients who were severely anoretic received 2 cc. of liver extract daily for varying lengths of time. While these patients comprise what is considered to be a control group, it is realized that refined liver extract contains vitamin B_{12} in small amounts[18] but

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† Eight ounces of high-protein milk formula contain 28 gm. protein and 343 calories.

‡ Each multivitamin tablet contained: vitamin A 5,000 U.S.P. units, viosterol 400 U.S.P. units, thiamin hydrochloride 2 mg., riboflavin 3 mg., nicotinamide 20 mg., and ascorbic acid 75 mg

the number of patients who received liver extract is small, and the amount of vitamin B_{12} contained therein is considered to be almost negligible. The patients in this group differed from the other 2 groups in that the majority of them received their treatment in the hospital annex. Strict attention could not be paid to the policy of bed rest because of the tremendous patient load which was handled at that time by relatively few doctors and nurses. It is felt that the patients in this group did not adhere to the policy of bed rest as well as did the patients in the main hospital.

TABLE 1.—COMPOSITION OF EACH OF 3 GROUPS OF 100 PATIENTS (TOTAL 300 PATIENTS) WITH HEPATITIS

Maximum Total Bilirubin mg./100 cc. serum	*Number of Patients*
1–5	36
5–10	30
10–15	25
15–20	6
More than 20	3
Total	100

Group II received only the prescribed hepatitis diet and bed rest. High-protein milk formula and intravenous glucose were judiciously administered to maintain the necessary caloric intake during the period of anorexia. The patients in Group III were treated in exactly the same fashion as those in Group II, except that vitamin B_{12} was given by mouth in the dose of 30 mcg. daily for the first 5 days of hospitalization. Ten patients in this group were given 30 mcg. of the drug by the intramuscular route once during the first 5 days of hospitalization. Gastric analysis on 20 patients in Group III revealed normal gastric acidity. There was no change in the quantity of hydrochloric acid secreted by these patients after vitamin B_{12} was administered by mouth for 5 days. It was assumed that the drug was absorbed when given by the oral route since it has been shown by Berk, *et al.*[3] that patients with pernicious anemia show satisfactory hematologic responses following oral administration of vitamin B_{12} with normal gastric juice.

Selection of patients for inclusion in this study was made on the basis of the maximum total serum bilirubin values recorded for 100 hepatitis patients who were in the vitamin B_{12} group. For example, there were 36 patients who received vitamin B_{12} who had maximum total serum bilirubin values 1 to 5 mg. per 100 cc. of serum. An equal number of patients having maximum values in the same range was selected from those who received the treatment outlined for Group I. Likewise, there are 36 patients in Group II whose maximum icterus fell into the same range. The other patients in Groups I and II were chosen in the same manner. There are, therefore, the same number of patients in each group and the same number in each of the ranges listed in Table I for the maximum total serum bilirubin.

ANALYSIS OF CHARACTERISTICS OF EACH GROUP. The duration of illness of each patient at the time of hospitalization was approximately the same. The mean duration of symptoms was 11.9 days in Group I, 11.3 in Group III, and 10.8 in Group II. Criteria for the selection of subjects for this study included suddenness of onset of illness, usually accompanied by chills or chilliness and fever, followed by clinical jaundice, in a group of young people who had no history of receiving blood or plasma. Hence all of the patients included in this study are believed to have had viral hepatitis of the IH type. A tabulation of all parenteral medications received by the subjects included in this report reveals that approximately the same number in each group received some kind of needle puncture during the 160 days preceding the onset of illness. The possibility of the inclusion of patients with serum hepatitis cannot be ruled out, but the type of onset and the pre-icteric phase of the disease suggest strongly that the etiologic agent was a virus of the IH strain rather than the SH.

Each patient was questioned, at the time of his initial history, about his possible exposure to hepatotoxins, including alcoholic beverages. The possibility of hepatitis due to such agents has been excluded as far as possible. The average intake of alcoholic beverages was tabulated and the over-all picture showed Groups I and II to be very similar, but the patients in Group

III tended to imbibe slightly more. The difference, however, cannot be regarded as significant.

The distribution of patients by age is practically the same for Groups I and II, the mean ages being 23.5 and 23.4 years, respectively. The mean age for Group III is 24.4 years, there being a few more people in this group who are in the 26 to 35 and the 36 to 45-year ranges. This difference is probably not significant, but it is well known that viral hepatitis is a disease of young people[16] and that it tends to be more severe in older patients[10]. The 3 groups are identical as regards racial distribution.

Many patients in Group III were given vitamin B_{12} because of their inability to eat and, as a group, they were sicker than the other 2 groups. This fact is illustrated by Fig. 1 which shows that a total of 83 persons in Group III had anorexia at the time of

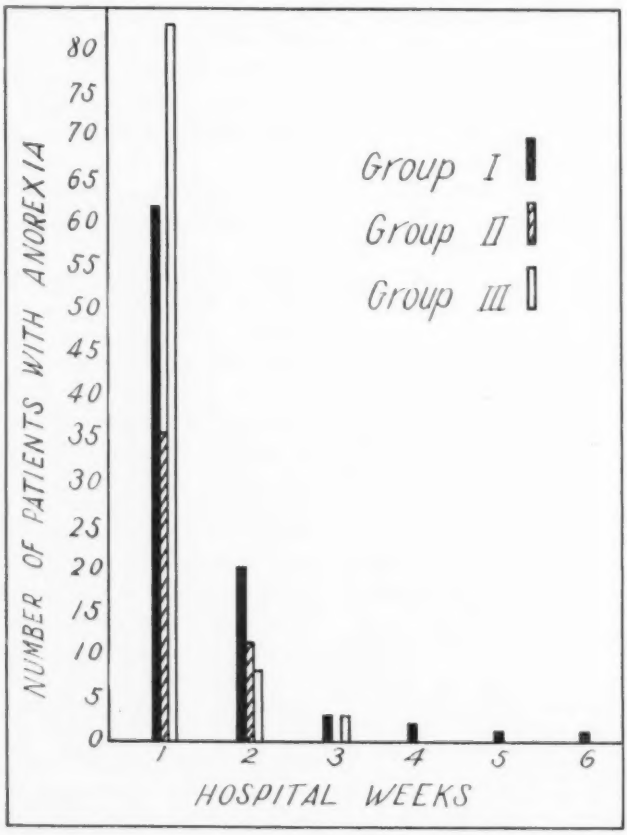

FIG. 1.—The incidence of anorexia by hospital weeks in 3 groups of 100 patients each. Group I was given bed rest, a high protein, high carbohydrate, moderate fat diet, brewer's yeast and multivitamins. Group II received the same diet and bed rest. Group III was treated in the same fashion as Group II with the addition of 30 mcg. of oral vitamin B_{12} daily for the first 5 days of hospitalization.

hospitalization as compared with 62 in Group I and 38 in Group II. The number of people having severe anorexia, graded 3 or 4 plus (Fig. 2), was greater in the vitamin B_{12} group. There were 19 persons with severe anorexia in Group III, as compared with 4 in Group I, and 2 in Group II.

ANALYSIS OF COURSE OF DISEASE IN EACH GROUP. At weekly intervals the patient's symptoms and signs were recorded by the ward doctor. Fig. I shows the effect of vitamin B_{12} on the appetite. The number of patients in Group III who had an inability to eat dropped from 83 to 8 during the first hospital week. The decrease is less striking in Group I, 63 to 20; and is 38 to 11 in Group II. There were 3 anoretic patients in Groups I and III during the third hospital week while the appetites of all patients in Group II had returned to normal. There were 2 patients in Group I whose anorexia continued through the fourth week and one had a subnormal appetite throughout the 9th week (not shown in Fig. 1).

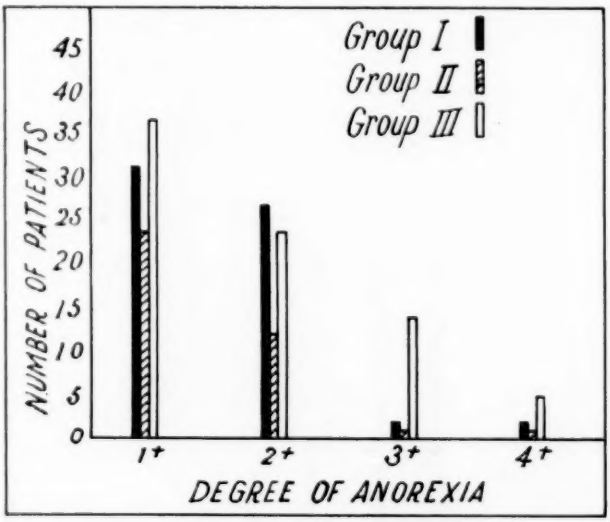

FIG. 2.—The degree of anorexia on admission in 3 groups of 100 patients each. (For a description of the groups, see Fig. 1.)

The incidence of hepatomegaly on admission as illustrated in Fig. 3 shows that more people in Group III had liver enlargement than in either of the other 2 groups. For statistical purposes, hepatomegaly was considered to be any enlargement of the liver of 1 cm. or more as measured below the right costal margin in the midclavicular line. Enlargement of the liver in an upward direction was not recorded. Seventy-two per cent of the patients who received vitamin B_{12} had larger than normal livers, whereas 58% of the patients in Group I had hepatomegaly and there were 54% with large livers in Group II.

Recovery from nausea, vomiting and malaise was rather prompt in all 3 groups. Bilirubinuria was recorded at weekly intervals, but it does not reflect the accompanying bilirubinemia, as has been pointed out by Watson[25],

Farquhar[6] and others; and because it has limited significance as regards the course of the illness, the data have been omitted from this report.

Fig. 3 shows the disappearance of hepatomegaly by hospital weeks. Group III shows the most striking drop, from 72 to 24, in the first week. Another precipitous drop in the number of patients in Group III who had enlarged livers occurred during the second week, from 24 to 6. The decrease in the number of persons in Group II who had liver enlargement was also quite striking with 54 during the first week and 19 during the second. The next interval showed a drop from 19 to 11. The decline in the number of patients in Group I who had hepatomegaly was more gradual, and after 11 weeks (not shown in Fig. 3) there was one patient who still had liver enlargement.

The large influx of patients, shortage of laboratory technicians, equipment, and other reasons, precluded performance of a complete battery of liver function tests on each patient at weekly intervals. It was found expedient to limit the laboratory tests of hepatic function to the total serum bilirubin during the icteric phase, and the bromsulfalein test was added during the post-icteric phase.

Determinations of the total serum bilirubin were done as soon as feasible after admission and at weekly intervals

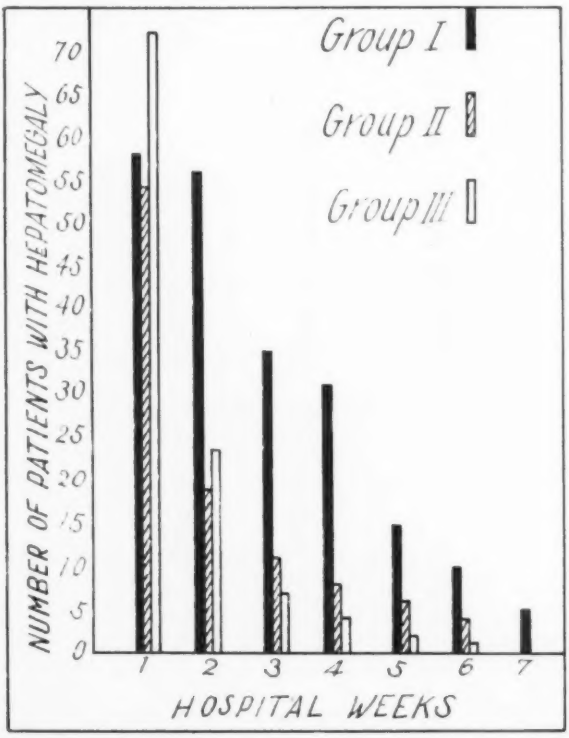

FIG. 3.—The incidence of hepatomegaly by hospital weeks in 3 groups of 100 patients each. (For a description of the groups, see Fig. 1.)

thereafter. The week during which the total serum bilirubin became normal (1.0 mg. per 100 cc.) is shown in Fig. 4. Of the patients in Group III, 73% had normal serum bilirubin levels 6 weeks after the onset of illness. Only 28 percent in Group II and 31 in Group I had normal tests. Ten weeks after the onset of illness all of the patients in Group III had normal values; 18 weeks were required for Group II and 24 weeks for Group I.

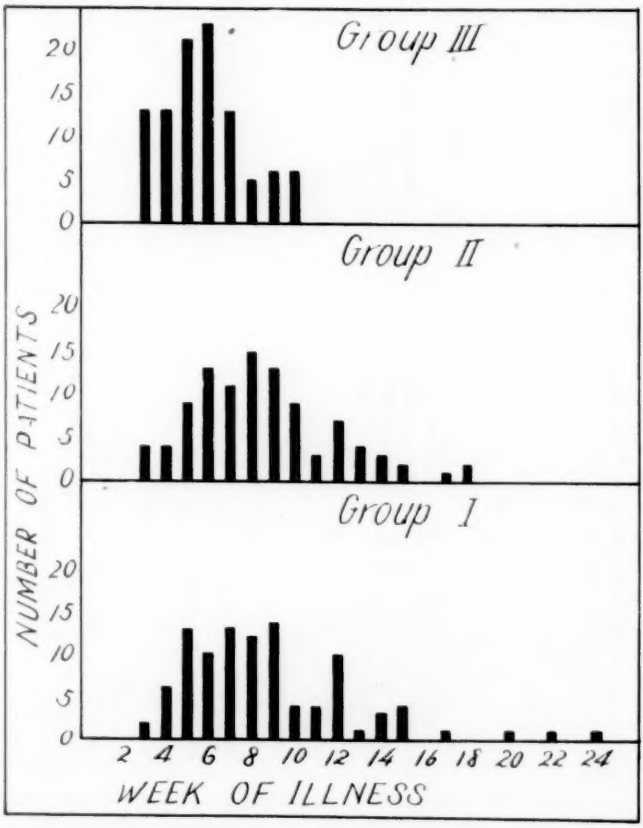

FIG. 4.—The week of disease in which the total serum bilirubin became normal (1.0 mg. per 100 cc.) in 3 groups of 100 patients each. (For a description of the groups, see Fig. 1.)

When the total serum bilirubin reached 2.0 mg. per 100 cc. or less, the percentage of bromsulfalein retention was measured and this determination was repeated at weekly intervals until the patient was discharged from the hospital. Five milligrams of dye per kilo. of body weight were injected intravenously and blood was drawn 45 minutes later[14]. These data, which appear in Fig. 5, show that all persons in Group III had normal bromsulfalein tests by the 13th week; all were normal in Group II by the 14th week, but 22 weeks had passed before all of the patients in Group I had normal tests.

When the total serum bilirubin reached 1.0 mg. per 100 cc. or less and the bromsulfalein retention was 5% or less, bed rest was terminated according to the criteria outlined by Capps and Barker[4]. Progressive ambulation was allowed to go on pass. After one week of such normal activity if the patient's tests remained normal, he was discharged from the hospital.

For statistical purposes the duration of illness was calculated from the date

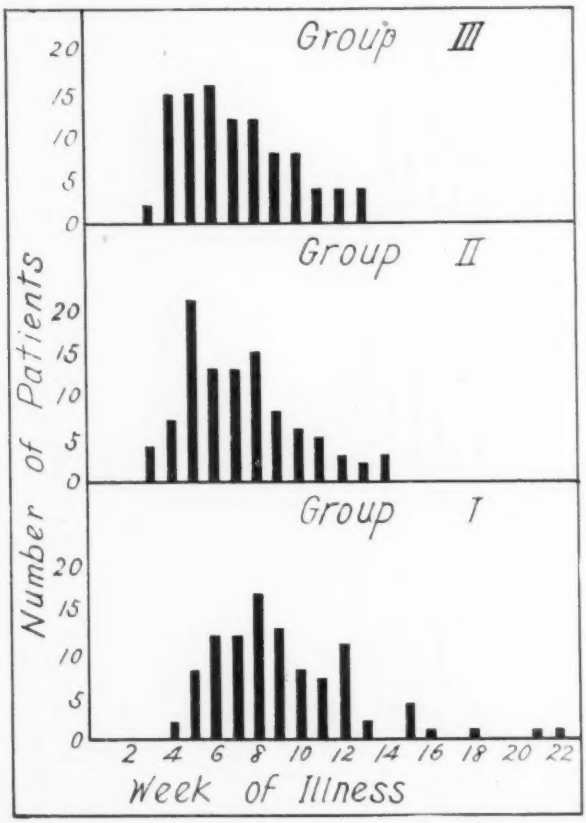

FIG. 5.—The week of disease in which the bromsulfalein became normal (5% or less) in 3 groups of 100 patients each. (For a description of the groups, see Fig. 1.)

consisted of allowing the patient to be up for one hour in the morning and one hour in the afternoon on the first day, increasing the period of ambulation by one hour each day, so that at the end of a week complete ambulation was reached. The patient's liver function tests were repeated at that time and if they were normal the patient

of onset of the first symptom to the date when the patient's laboratory tests became normal and remained so. Comparison of the 3 groups as to duration of illness is shown in Table 2. Fifty-one per cent of the people in Group III recovered from their illness in the 20 to 45 day period as compared to 38% in Group II and 29% in Group I.

The mean duration of illness was 48.7 days for the people in Group III, 54.4 days for those in Group II and 58.7 for the patients in Group I. There were 5 instances in Group I in which patients' total serum bilirubin or bromsulfalein retention tests, or both, became abnormal after ambulation was begun. Bed rest was reinstituted in these instances and the patients were considered to have had relapses. Five such relapses occurred in Group I; there were 4 in Group II, and 2 occurred in Group III.

TABLE 2.—DURATION OF ILLNESS* IN THE THREE GROUPS

Duration of Disease (Days)	*Number of Patients*		
	Group I	*Group II*	*Group III*
20–45	29	39	51
46–60	34	27	25
61–75	14	14	10
76–90	15	10	11
91–105	0	5	3
106–120	4	1	
Over 120	4	4	
Total	100	100	100

* The duration of illness was calculated from the date of onset of the first symptom to the date on which the liver function tests returned to normal and remained so.

Discussion. The data presented in the previous sections show that the patients who received vitamin B_{12} as part of their treatment recovered from their illness at a more rapid rate than those who did not receive it, and they did so in spite of having the disease in more severe form. As has been previously stated, the supervision of the patients in Group I as regards bed rest was inadequate, and their poor showing is believed due partially to this fact. In many instances the sicker of the patients who were admitted to the hospital during the time this work was done were given vitamin B_{12} and those who did not receive it were treated with diet and bed rest alone. The patients in the latter category (Group II) could, therefore, reasonably be expected to recover more rapidly than a more homogeneous group such as Group I. It is not believed that the multivitamins and brewer's yeast, which the Group I patients received, were in any way responsible for their delayed recovery. It is known that in experimental animals fatty livers can be produced by large doses of thiamin[15], but it appears to have no application to this situation.

For its inclusion in the therapeutic armamentarium of viral hepatitis a drug should have one of 2 prerequisites. It should have an ameliorative effect on the process of recovery itself, or improve the patient's sense of well-being so that the processes of repair are secondarily stimulated. Vitamin B_{12} certainly qualifies in the latter respect. *When it is given by the intramuscular route its effect on the appetites of anoretic hepatitis patients is dramatic.* It is not at all unusual for a severely anoretic hepatitis patient to regain his appetite in 24 to 72 hours after receipt of 30 mcg. of vitamin B_{12} by the parenteral route. The response to the oral preparation is not as definite but occurs in 2 to 5 days.

There are many reports in the literature which suggest that it has a direct influence on the recovery process. It has been found that vitamin B_{12} has significant lipotropic activity in rats which are maintained on a low-protein, low-fat diet[7]. This effect was greatly enhanced by the presence of methionine. The synergistic effect of vitamin B_{12} with methionine was partially clarified by Jukes *et al.*[11], who showed that vitamin B_{12} deficient chicks are unable to transform homocystine into methionine, whereas normal chicks are able to do so and, consequently, vitamin B_{12} is involved in this transformation. Dubnoff[5] demonstrated a greater synthesis

of methionine from homocystine in the presence of vitamin B_{12}, using liver slices. The degree of glutathione reduction was similarly affected. These results suggest that, in addition to catalyzing transmethylation reactions, vitamin B_{12} might also be involved in a wide variety of enzyme systems, namely, those involving S-S and S-H groups.

It has been shown that large doses of vitamin B_{12} protect the ribonucleic acid content of liver cells of rats poisoned with carbon tetrachloride[12]. Horrigan *et al.*[9], in their work on the local instillation of vitamin B_{12} into the bone marrow have demonstrated a further link with nucleoprotein metabolism. Thorell[23] showed that normally, during the growth process of granulocytic and erythroid precursor cells, the formation of new cellular protein is associated with a rise in the ribonucleic acid content of the cytoplasm and nucleus. As growth activity decreases, the concentration of ribonucleic acid decreases proportionately. In normal erythropoesis hemoglobin formation does not begin until the ribonucleic acid metabolism has been completed. In pernicious anemia hemoglobin synthesis begins while the ribonucleic acid content of the cell is still high. This abnormality is corrected by the instillation of vitamin B_{12} into the bone marrow.

It has been shown that thymidine (thymine nucleoside) can be substituted for vitamin B_{12} in the growth of *Lactobacillus lactis* (Dorner) and for APF[20,21] in the nutrition of *Lactobacillus leishmanii*. These observations have led Vilter *et al.*[24] to suggest that vitamin B_{12} may catalyze a reaction which results in the formation of thymidine.

Large quantities of thymine in the presence of purines will replace folic acid as a growth factor for *Streptococcus faecalis R* and *Lactobacillus casei*[21,22]. Desoxyribonucleic acid is produced in subnormal quantities by *L. casei* if the folic acid content of the media is reduced[17], but this defect can be overcome by the addition of thymine.

From these pieces of experimental evidence, a relationship between vitamin B_{12} and folic acid in nucleoprotein metabolism becomes evident. Vilter *et al.*[24], have postulated a series of reactions by which nucleic acid is formed. Beginning with simple nitrogen- and carbon-containing substances, the roles played by folic acid and vitamin B_{12} as catalysts have been outlined by these workers.

Since it has been shown that vitamin B_{12} is involved in transmethylation reactions, that it may be involved in enzyme systems employing S-S and S-H groups and it is intimately associated, along with folic acid, in nucleoprotein metabolism, it is inevitable that vitamin B_{12} should be employed in the processes of hepatic repair.

No attempt has been made to determine the statistical significance of the results because it is felt that there are too many factors involved which would tend to limit the meaning of any statistical calculation. For example, the method of selecting patients for this study is objectionable because they were not chosen at random. There were no simultaneous controls receiving placebo preparations resembling vitamin B_{12}. On the other hand, this work was carried out in a military installation in the Zone of Communications under war-time conditions and all of the factors necessary for a well-controlled research project were not present.

This investigation indicates that vitamin B_{12} may hasten the recovery from viral hepatitis. Further investigation in this field of therapy appears warranted. Its close association with folic acid suggests the possibility that the addition of the latter drug to the therapeutic regimen for hepatitis would make the

treatment even more effective. This premise is being investigated and the results will be reported in the near future.

Summary. Three groups of 100 patients each, who had acute viral hepatitis, have been compared with respect to clinical course, duration of illness and incidence of relapse. The groups were comparable as regards age, race, duration of illness and degree of icterus. Group I received the conventional treatment consisting of a high-protein, high-carbohydrate, moderate-fat diet, bed rest, multivitamins and brewer's yeast. Group II received the same diet and bed rest without added vitamins or brewer's yeast. Group III received the same treatment as Group II but with the addition of 30 mcg. of vitamin B_{12} by mouth daily for the first 5 days of hospitalization. The following results were observed:

1. The patients who received vitamin B_{12} had a more rapid return to normal appetite and liver size than did the patients in the other two groups.

2. The total serum bilirubin values of all of the patients in the vitamin B_{12} group were normal after the 10th week of illness, whereas 18 weeks were required by Group II, and 24 weeks by Group I.

3. The mean duration of illness, calculated from the date of the onset of the first symptom to the date the liver function tests became normal and remained so, was 48.7 days for the patients who received vitamin B_{12}, 54.4 days for those who received the prescribed diet and bed rest only and 56.7 days for those who received the conventional regimen for hepatitis.

4. There were 5 instances of relapse in the latter group, 4 such instances in the group receiving diet and bed rest and only 2 among the patients given vitamin B_{12}.

5. Experimental work links vitamin B_{12} to nucleoprotein metabolism and, hence, liver repair. Its role as a lipotropic agent is further evidence of its importance in liver diseases. The relationship of vitamin B_{12} to folic acid in this process is considered.

6. Possible objections to the validity of the results obtained herein are raised, but it is concluded that the results are sufficiently suggestive as to warrant further investigation.

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THE RELATIONSHIP OF BILIARY TRACT DISORDERS TO DIABETES MELLITUS

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Diabetics have long been known to have a high incidence of biliary tract disorders. It is the purpose of this article to review and to illustrate how diabetes mellitus may be caused or aggravated by disorders of the biliary tract. The effect of the biliary tract upon diabetes is dependent upon (a) the anatomic and physiologic relationships of the biliary tract and the pancreas and (b) the effect of functional disorders and organic disease of the biliary tract upon the pancreas. An accumulated clinical experience now justifies conclusions as to how an adequate management of such conditions may have therapeutic value for the diabetic.

The high incidence of biliary tract disorders preceding diabetes has been shown statistically by Rabinowitch[26]. Joslin[14] stressed the danger to the diabetic of cholelithiasis, biliary tract infection, pancreatitis and liver disease. This author stated that in autopsies on 65 diabetic patients with gallbladder disease, the latter condition was considered to be the cause of death in 6.

Incidence. The fact that many diabetics have chronic cholecystitis or cholelithiasis has been noted by Joslin[14]. Tedstrom[29] found cholecystographic evidence of gallbladder dysfunction in 44% of 70 diabetics over age 40. Rabinowitch[26], in a biometrical study, found: 1) In patients with disease of the gallbladder and its passages, 9 times as many had diabetes as would be expected. 2) The incidence of diabetes was greater in cholecystitis than in cholelithiasis. 3) In acute pancreatitis the incidence of diabetes was 40 times that of chance.

Cholelithiasis has been found at autopsy in 31% of diabetics, with an incidence of 21% in a control series of non-diabetics[32]. Bockus[3] estimated the incidence of cholelithiasis in the average population of the United States to be 10%. Of the 31% of diabetics having cholelithiasis, the condition was recognized clinically in 5%[14].

Pancreatitis, also shown by Rabinowitch[26] to have a high incidence in diabetes, was noted by Bockus[3] to be preceded in most cases by cholelithiasis. Rabinowitch[27] furthermore stated that infection of the biliary tract is a common precursor of the pancreatitis which sometimes precedes diabetes mellitus and that the onset of the gallbladder disease is usually earlier than that of diabetes. A similar viewpoint has been expressed by Jordan[13], Judd[23], Deaver and Sweet[6] and others[14]. Carter[4] in a review of 213 personal surgi-

* Dr. Carter died on April 19, 1952.

cal cases of acute cholecystitis, found evidence of acute pancreatic involvement in 28 (13%) with subsequent development of diabetes in some cases. Schumaker[28] estimated that from 3 to 10% of patients with acute pancreatitis became diabetic.

one of the most important etiologic factors in diabetes mellitus." Allen[1] furthermore concluded: "Statistical data and circumstantial evidence in individual cases indicate that diabetes may be secondary to cholelithiasis and infection of the biliary tract." Rabino-

FIG. 1.—Cholecystcholangiogram in a patient with acute cholecystitis who developed an acute pancreatitis, with obstruction of the common bile duct.

ETIOLOGIC FACTORS IN DIABETES. In diabetics having biliary tract disorders, evidence clearly indicates that in certain patients the biliary disorders preceded the onset of the diabetes[14]. Jordan[13] stated that in a series of patients having both conditions the average duration of the gallbladder symptoms preceded the onset of the diabetes by 12.9 years. Jones[9] has stated: "In adults, cholelithiasis is probably

witch[26] also found "a causal relationship between disease of the gallbladder and diabetes mellitus."

Notwithstanding the above facts, it should be emphasized that in some diabetics with biliary tract disorders, there is no apparent relationship between the two conditions. In other patients with biliary tract disorders who develop diabetes, this sequence of events is apparently dependent up-

on the inter-relation of definite anatomic and physiologic factors.

Anatomic Factors. Significant features of the anatomic arrangements are 1) the path of the common bile duct through the head of the pancreas and 2) the common opening of the pancreatic and common bile ducts above the sphincter of Oddi. Hjorth[10], on the basis of anatomic and cholangiographic studies in large series of individuals coming to autopsy, concluded that over 80% showed a common opening of this type.

The above anatomic arrangements may cause biliary tract obstruction by enlargement of the head of the pancreas. In the patient referred to in Fig. 1, there was an acute pancreatitis secondary to chronic biliary tract disease which aggravated the biliary tract disease by secondary obstruction. Such obstruction is known to predispose to biliary stasis, infection, possible stone formation and subsequent aggravation of the pancreatitis which may be a precursor to diabetes. Allen[1] among others stressed the fact that inflammation, tumors or enlargement of the glands in the head of the pancreas may cause pressure upon the common bile duct, resulting in obstructive jaundice and liver disease.

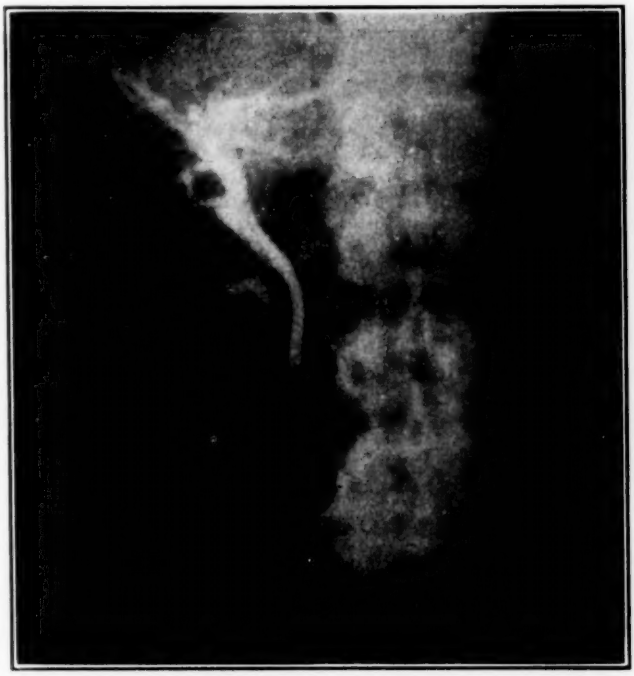

Fig. 2.—Cholangiogram showing calculus in a position to obstruct both the common and the pancreatic ducts, with visualization of the pancreatic duct after injecting dye into a bile duct.

The common opening of the biliary and pancreatic ducts may permit a single lesion to block both ducts, with resulting pathologic changes in either or both systems. An illustrative case is shown in Fig. 2, where a calculous obstruction of the ampulla of Vater has

caused a regurgitation of dye from the biliary tract into the pancreatic duct. The presence of bile in the pancreas of patients with pancreatitis has been demonstrated by Colp and Doubilet[5] and others.

Associated physiologic disturbances furthermore have been found to occur in the pancreas as the result of biliary tract disorders. Berger and Schnetz[2] investigated 115 patients with chronic gallbladder disease having symptoms suggestive of pancreatic disease. The majority showed deficiencies in the external secretion of amylase, lipase and protease. There was also evidence of a disturbance in the internal pancreatic secretion, in that half the patients showed a hyperglycemic and half a hypoglycemic tendency. Jones *et al.*[12], in a series of diabetics, also found in nearly half the evidence of abnormal external pancreatic secretion, as shown by alterations in the amount of lipolytic and proteolyic enzymes in the duodenal content.

Another type of obstructive lesion is shown in Fig. 3. Here in 2 patients there was visualization of the pancreatic duct by dye injected into the common duct, where operation revealed no apparent cause for this, other than spasm of the common duct sphincter. The spasmodic character of the obstruction was confirmed by the fact that in only one plate was the pancreatic duct visualized in a series of cholangiograms.

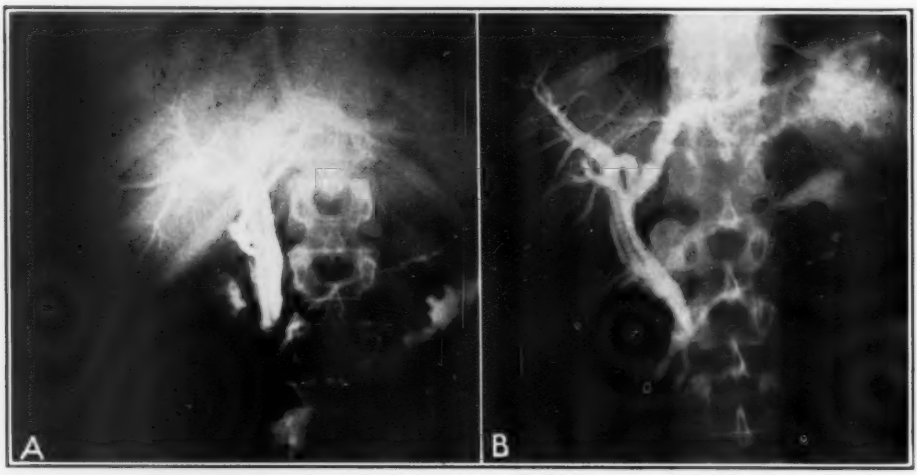

FIG. 3.—Cholangiograms in 2 patients having common communications between the pancreatic and common bile ducts. The pancreatic ducts are visualized because of persistent common duct sphincter spasm, when dye is injected into the common duct.

Another illustration of the importance of persistent common duct sphincter spasm is shown in Fig. 4, where a delayed cholangiogram 2 weeks after an operation for pancreatitis revealed a regurgitant visualization of the pancreatic duct with a dilatation of both the pancreatic and common bile ducts. Our own experience in this regard is in accordance with that of Colp and Doubilet[5], who have stated that obstruction of both ducts may occur as the result of a single lesion, such as calculus, spasm or inflamma-

tion of the common duct sphincter, tumors of the ampulla of Vater or duodenum, duodenitis or diverticulum of the duodenum.

Generally speaking, the end results of interference in emptying of the common bile duct may be: 1) biliary stasis with a predisposition to activation of an existing infection, 2) progressive infectious disease of the bile ducts with ultimately liver and pancreatic involvement, 3) stone formation which in turn may be an additional obstructive element. In patients with a common opening of the pancreatic and common bile ducts obstructive lesions at the ampulla of Vater may give: 1) biliary reflux of pancreatic secretion into the bile ducts and gallbladder, 2) pancreatic reflux of bile into the pancreatic ducts, 3) pancreatitis with possibly a subsequent diabetes. The diseased conditions of the biliary tract and pancreatic ducts described result for the most part primarily from physiologic changes in the biliary tract which may precede the onset of organic conditions found at the time of the diabetes or occur during the course of the disease. Thus the changes in the biliary tract and pancreatic disorders may be consider-

FIG. 4.—Delayed cholecystcholangiogram, taken 2 weeks after an operation for acute pancreatitis, showing filling and distention of the pancreatic and common bile ducts. The dye is injected through the cholecystostomy tube.

ed either as etiologic factors or agents which may aggravate concomitant diabetes.

ASSOCIATED PATHOLOGIC CONDITIONS OF THE BILIARY TRACT. Pathologic changes in the biliary tract which may precede or accompany diabetes are: sphincter spasm, infectious cholecystitis, cholangitis, cholelithiasis, cancer of the gastrointestinal tract and benign or malignant lesions of the biliary tract. Concomitant liver changes may be hepatitis, fatty infiltration of the liver or portal cirrhosis. The frequency with which cholelithiasis is found in the other conditions noted makes the high incidence of calculi in diabetes of particular significance. Hyperglycemia but not glycosuria was found in 80% of one series of patients with cholelithiasis[27].

The fatty liver of uncontrolled diabetes is associated with a deficiency of liver glycogen, a high blood and urine sugar and a great increase in the insulin requirement[9,14]. With control of the diabetes the fatty infiltration is reduced, the glycogen reserve restored and the insulin requirement usually lowered[15].

INFECTION. Infection of any type is serious in the diabetic, increasing greatly the insulin requirements and the difficulties in management[16,28]. Furthermore, infection of the biliary tract is particularly dangerous because of 1) the frequency of its association in calculous obstruction, 2) the resultant liver damage, 3) the concomitant metabolic disturbances of the diabetes, 4) the drainage of the biliary tract lymphatics to the lymph nodes in the head of the pancreas, and 5) the fact that in the diabetic chronic biliary tract infections are seldom recognized[14]. Eisele[7], in a review of 76 diabetic patients having operations upon the gallbladder, found 6 cases of acute cholecystitis or empyema of the gallbladder, with 9 perforations, a 14% incidence of perforation, as compared with 1% in non-diabetics.

CANCER. There has been recently an increase in the incidence of cancer in the diabetic. This increase was 3 to 4 times that found in the general population from 1914 to 1946. During this period the average age at death of the diabetic increased from 46.5 to 64.5 years[19]. Operation upon the 75 diabetics reported by Eisele[7] showed 8 carcinomas of the pancreas and 2 of the gallbladder, a 14% incidence of malignancy.

In 243 diabetic patients dying of cancer, Joslin[18] found 14 carcinomas of the liver and 33 of the pancreas, and the latter incidence was exceeded only by 35 carcinomas of the breast. Joslin stated that carcinoma of the pancreas was found to account for 12 to 13% of the cancer deaths in diabetics, as contrasted to 2.5% of cancer deaths in the general population of Boston.

Statistical studies[8,11,24] have shown a higher general incidence of cancer in diabetics, especially in obese males. The fact that the history of diabetes is almost invariably of much longer duration than that of cancer indicates that cancer of the biliary tract or the pancreas is a complication rather than an etiologic factor in diabetes[19].

The mechanisms whereby disorders of the biliary tract may predispose to or aggravate diabetes are illustrated by the following patients:

Illustrative Case Reports. CASE 1. C.G., a female aged 53 years, was admitted July 22, 1951. Following recurrent attacks of right upper quadrant pain of 6 months' duration, there had been a severe attack radiating to the right flank for 36 hours before admission. With this there had been nausea, vomiting and dark urine. The past history revealed a cholecystectomy in 1927, a choledochotomy for common duct stones in 1942.

Upon admission the temperature was 102.4°, the pulse rate 100. There were tenderness and spasm of the right upper quad-

rant. The serum bilirubin was 1.6 mg. per 100 cc., the cholesterol 216 mg., esters 130 mg. The alkaline phosphatase was 6.9 Bodansky units, the serum amylase 5.3 units (Normal 1 to 2.5 units). The leukocytes were 8000, the polymorphonuclear count 90%. The urine was negative. Cultures of the duodenal bile showed an enterococcic type of streptococcus.

At laparotomy there was found peritonitis with free bile in the peritoneal cavity, fat necrosis and acute pancreatitis. The bile peritonitis was due to a perforation of the common bile duct, which was filled with stones and "mud." Cultures of the common bile and stones showed the same type of streptococcus found in the duodenal drainage bile.

The operative cholangiogram showed a dilatation of the common and intrahepatic bile ducts, with an elongated spastic papilla as shown in Fig. 5.

Following operation the patient made an uneventful recovery. However, when seen by Dr. Benjamin Ashe on Oct. 19, 1951, she was found to have diabetes mellitus. There was at that time 2% sugar in the 24-hour specimen of urine, the blood sugar was 250 mg. per 100 cc. (Folin-Wu). Following dietary management only, the diabetes was controlled. The 24-hour specimen of urine showed only a trace of sugar and the blood sugar was 150 mg.

This patient illustrates a chronic recurrent infectious cholecystitis and cholangitis, with stones and common duct obstruction which resulted in acute cholecystitis, cholangitis and subsequently diabetes. The factor which apparently determines whether or not diabetes follows the pancreatitis is the amount of pancreatic necrosis and the degree of destruction of the Islands of Langerhans.

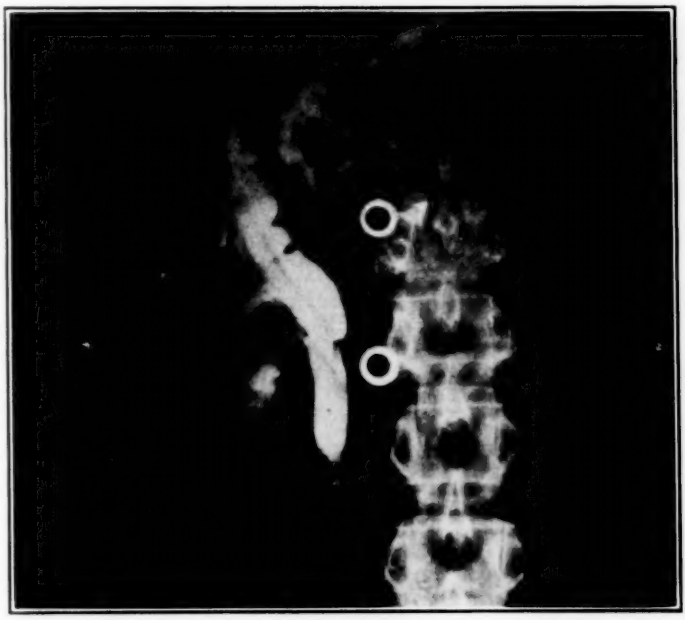

FIG. 5.—Operative cholangiogram in a patient with acute pancreatitis, showing spastic common duct sphincter, extrinsic pressure on the common bile duct and dilatation of the extra- and intra-hepatic bile ducts.

That surgery may also be of therapeutic value in the diabetic with persistent biliary tract disorders not relieved by medical therapy is shown by the following case:

Case 2. M.A., a female, aged 35 years, was first seen in 1939. She had been known to be a diabetic since 1925. A cholecystectomy had been done elsewhere in 1934, without benefit to the diabetes. Following cholecystectomy there had been recurrent attacks of right upper quadrant colic with nausea and vomiting. These attacks were not relieved by intensive therapy with sedatives and antispasmodics. Jaundice appeared in 1937, following an unusually severe attack. The patient was then admitted to another hospital, with the diagnosis of a common duct stone. At operation the common duct was dilated but no stone was found. The operation consisted of a choledochostomy and "T" tube drainage. Following the operation there was a constant dull pain in the right upper quadrant, with recurrent acute attacks as before. The daily insulin requirement was from 60 to 90 units.

Upon admission to our hospital in 1939 the diabetes was found to be uncontrolled with 90 units of insulin daily. After 18 days of treatment the daily insulin was reduced to 30 units. At operation the common duct was found to be dilated, there were no stones or apparent pathologic conditions of the ampulla of Vater. The liver and pancreas were normal in appearance. A choledochoduodenostomy was performed.

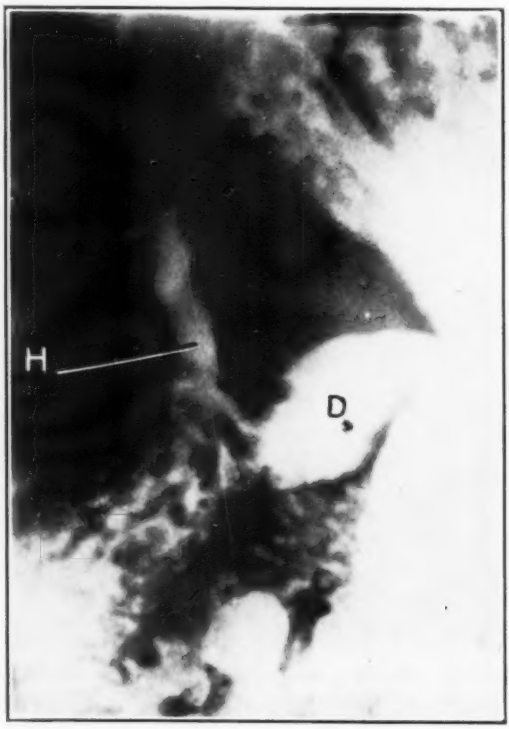

Fig. 6.—Gastrointestinal roentgenogram showing the duodenum and common hepatic duct, taken 4 years after operation of hepaticoduodenostomy upon a diabetic patient having recurrent attacks of pain and jaundice following cholecystectomy and a previous choledochostomy. The common hepatic bile duct is seen at "H", the duodenum at "D".

Since operation the patient has remained well, there have been no further attacks of pain or jaundice. The "T" tube was left in for 56 days. The gastrointestinal series now visualizes the common bile duct, indicating a patent anastomosis. (Fig. 6). Similar findings were reported in the delayed cholangiogram. Tests of liver function are normal. The glycosuria is controlled on dietary treatment only.

This patient illustrates 1) recurrent colic and jaundice due to severe chronic and persistent spasm of the common duct sphincter, 2) the apparent aggravation of pain by the previous surgical removal of the gallbladder, 3) the failure of previous medical therapy and choledochostomy to relieve the recurrent attacks of colic, and 4) the apparent permanent value of choledochoduodenostomy in the improvement of the diabetic condition.

Joslin[20] had suggested the possible therapeutic value of a choledochoduodenostomy as the result of an experience with a woman in whom a diabetic condition practically cleared up during a period of common bile duct drainage, only to recur when the drainage was stopped.

Surgical Considerations. The presence in the diabetic of organic infectious or obstructive biliary tract disease is an indication for surgery. It has also been shown that the presence of persistent functional disorders of an obstructive nature may be benefited by surgery. The early recognition and relief of such conditions may prevent unfavorable progression of the biliary tract disease and at the same time diminish the likelihood of complications, such as acute cholecystitis or pancreatitis. Furthermore, the surgical correction of such conditions may lessen the severity of the diabetes.

Since, with biliary tract disease, the diagnosis of the pancreatitis which may precede or aggravate diabetes is seldom made clinically, the possibility of this condition should always be kept in mind. Among confirmatory laboratory tests, those of the serum amylase and lipase are probably most useful.

We are in agreement with Joslin that, whenever possible, operations upon the biliary tract are best performed during intervals of freedom from symptoms, when it is possible to have the general condition of the patient favorable and the best of surgical and anesthetic services available.

Due recognition must also be given to the fact that there may be an increased risk of operation in the diabetic due to the presence of unrecognized heart disease. The almost universal presence in advanced diabetes of severe generalized arteriosclerosis and coronary disease has been noted by Joslin[16]. Eisele[7] found that the incidence of coronary occlusion in diabetics over the age of 50 was 3 to 5 times that of non-diabetics. He has attributed some failures in biliary tract operations to the presence of unrecognized advanced coronary disease. The principles of surgical management of the cardiac patient with biliary tract disease has been reviewed by Twiss and Carter[30].

Provided the presence of recent myocardial failure or infarction has been ruled out, the risk of operation in diabetics has proved to be no greater than that of non-diabetics[22]. This result can be considered and assured, however, only with the cooperation of the most competent and experienced of surgeons, internists and anesthetists.

The results of surgery in the diabetic are dependent upon the degree of pathologic change in the biliary tract and pancreas at the time of operation, the severity of the diabetic condition and the adequacy of surgical and medical care in the control or correction of basic disorders in the biliary and pancreatic ducts.

Clinical Applications. In view of the foregoing facts, it is obvious that diabetic patients with digestive symptoms should have the benefit of a comprehensive diagnostic investigation of the biliary tract and pancreas. This should include a cholecystogram. A

properly-performed duodenal drainage may furnish valuable confirmatory evidence of a non-functioning gallbladder or give evidence of pancreatic dysfunction. Cultures of duodenal bile furthermore afford the most reliable evidence of biliary tract infection, as proved by subsequent cultures of the biliary tract taken at operation[31]. Tests of pancreatic and liver function are also useful. Roentgen-ray studies of the gastrointestinal tract may also give evidence of pancreatic involvement[25].

The early recognition and diagnosis of biliary tract disorders is a great advantage in the medical management of the diabetic. The presence of pain, nausea, vomiting and fever greatly complicates the dietary management and increases the insulin requirements. Proper surgical therapy will frequently permit the use of a more liberal diet and lower the insulin requirement.

Summary and Conclusions. 1. Biliary tract disorders of an infectious, calculous or functional obstructive nature may result in diabetes mellitus or pancreatitis with subsequent diabetes.

2. The anatomic, physiologic and pathologic features of biliary tract disease which may predispose to or aggravate diabetes are discussed and illustrated.

3. The early recognition and surgical correction of such lesions may have an important prophylactic or therapeutic effect in diabetes.

4. In the diabetic properly controlled, the risk of competent surgery is not greater than in the non-diabetic.

5. Since the degree of pathologic changes in the biliary tract and pancreas cannot be ascertained with accuracy clinically, the pre-operative prognosis in these cases should be guarded.

The authors are indebted to Doctor Benjamin Ashe for a review of this text.

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PLATELET AGGLUTINATION BY AN ABNORMAL PLASMA FACTOR IN THROMBOCYTOPENIC PURPURA ASSOCIATED WITH QUINIDINE INGESTION*

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Thrombocytopenic purpura has occasionally been observed during treatment with a wide variety of drugs[6,7,19] including quinine[8,19], but purpura in association with the latter's stereoisomer, quinidine, has only recently also come to attention. Thus, a review of the literature discloses reports of at least six cases[5,9,12,13,14,15] of quinidine-induced thrombocytopenia since 1941.

The mechanism of drug-induced thrombocytopenia is obscure and has usually been ascribed to hypersensitivity. However, Grandjean[8] has described *in vitro* lysis of platelets in the plasma of a quinine-sensitive patient on addition of this drug, and Ackroyd[1,2,3,4] has recently clarified some aspects of thrombocytopenia induced by the drug sedormid. He observed that there was marked *in vitro* agglutination of the platelets of sedormid-sensitive patients in the presence of this drug, and that there was subsequent platelet lysis and reduced clot retraction. Essential for platelet agglutination and lysis by sedormid was an abnormal factor in the patient's plasma. The factor was active against both normal platelets and those of the patient, while the patient's platelets were unaffected by sedormid in normal plasma. These observations suggest that sedormid-induced thrombocytopenia was preceded by *in vivo* platelet agglutination and lysis. Ackroyd further observed that local application to the skin of a suspension of sedormid crystals in a saturated solution of sedormid in propylene glycol induced purpura confined to the treated area, but not general thrombocytopenia.

That platelet destruction or agglutination and removal from the circulation may occur in the thrombocytopenia associated with quinidine may be inferred from the extreme rapidity of platelet decline following test doses of this drug. Marked decreases in platelet numbers in the venous blood have been reported within ½ hour after the oral administration of quinidine[12]. Since the normal life span of the platelet is at least 24 hours and probably extends to from 4 to 6 days[10,11,18], it is apparent that depression of the megakaryocytes cannot readily explain so rapid an effect of quinidine. Hirsch and Dameshek[9] have presented evidence in a quinidine-sensitive patient both of platelet destruction and of al-

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teration in the morphology of the megakaryocytes of the bone marrow.

In the following report we present studies of platelet agglutination in plasma derived from 2 patients who developed thrombocytopenic purpura following treatment with quinidine.
We are indebted to Dr. B. M. Jacobson for the opportunity to study Case 1, and to Dr. W. C. Moloney and Dr. E. G. Auld for permitting us to examine Case 2.

Case Reports. CASE 1. A 56-year old woman was admitted to another hospital for study of a variety of symptoms involving the cardiorespiratory and gastrointestinal systems. The patient had been taking quinidine daily for almost 2 years, and on admission the stained blood smear contained a normal proportion of platelets and eosinophils. Her treatment included medication with phenobarbital, demerol (meperidine hydrochloride), chloral hydrate, thyroid substance, aspirin, atropine, priodax (β-(4-hydroxy-3), 5 - diiodophenyl) - α - phenylpropionic acid), and quinidine. The only medicine consistently administered was quinidine, and on the sixth hospital day the patient developed generalized purpura, epistaxis, and bleeding gums. Platelets were absent from the smear and an eosinophilia of 10% was present. The sternal marrow aspirate contained increased numbers of eosinophilic myelocytes. Megakaryocytes were present in approximately normal numbers, but showed no evidence of platelet production. On this day all prior medication was stopped, a transfusion was given, and the parenteral administration of adrenocorticotropic hormone (ACTH) was begun at the rate of 80 mg. per day in divided doses. By the following day, the gums had stopped bleeding and the platelet count (indirect) was 42,000 per c.mm. Thereafter recovery was rapid. The ACTH was discontinued after 3 days.

When first seen by us on the third day after the onset of purpura, mucous membrane bleeding had ceased, although fading purpura and ecchymoses were still visible. Capillary fragility and clot retraction were normal, and the platelet count (direct) was 134,000 per c.mm. Red and white cell counts, hematocrit, hemoglobin concentration and stained blood film were normal. The whole blood coagulation time[16] and prothrombin concentration[17] were normal. Normal prothrombin time was observed in serum incubated 24 hours at 37.5°C., using barium sulfate plasma as prothrombin-free diluent. Although the patient's plasma clotted with normal rapidity on addition of thrombin, the dissolution of such a clot within 24 hours at 37.5° indicated the presence of increased fibrinolytic activity. Three days later, the platelet count (direct) was 326,000 per c. mm. and the fibrinolysin had disappeared.

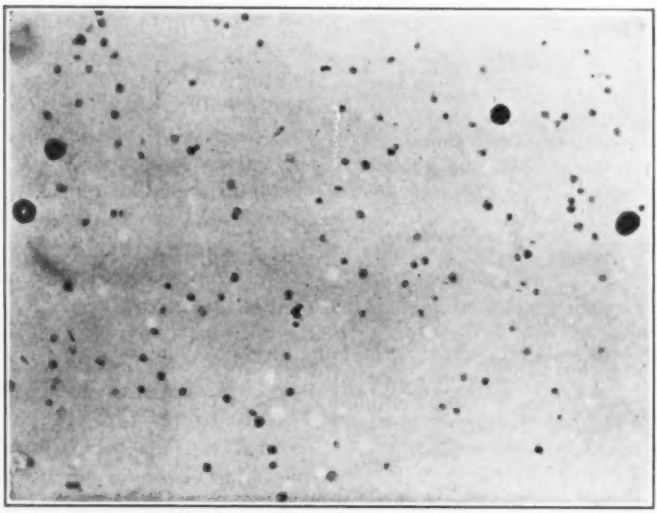
OBSERVATIONS OF PLATELET AGGLUTINATION IN CASE 1. In an effort to discover the *in vitro* reaction of the patient's platelets to the several drugs administered, a sample of double-oxalated whole blood was secured with silicone coated apparatus on the sixth day after onset of purpura. Platelet-rich plasma, obtained after centrifugation at 200 g for 5 minutes, was divided into 6 portions of 1 cc. each. Five of these were diluted with 0.1 cc. of a solution in physiologic saline of each of the 5 drugs listed in Table 1. The final concentration of each drug in the mixture approximated 10 mg. per 100 cc. The sixth portion of the patient's platelet-rich plasma was diluted with 0.1 cc. of physiologic saline solution devoid of any drug. The reaction of each platelet suspension was then adjusted to pH 7.35 by equilibration with a gas mixture of 5% CO_2 and 95% O_2. Thereafter the 6 mixtures were shaken mechanically for 1 hour at room temperature. A total of 500 individual platelets, including both separate platelets and those in clumps, was counted in consecutive microscopic fields of Wright-stained smears from each sample. The number of agglutinated platelets (more than 2 platelets in contact) was recorded and related to the total number of platelets counted as a percentage. As a control for the method, a sample of the platelet-rich plasma of a normal person was treated in exactly the same fashion.

The result of this study is presented in Table 1, which reveals good agree-

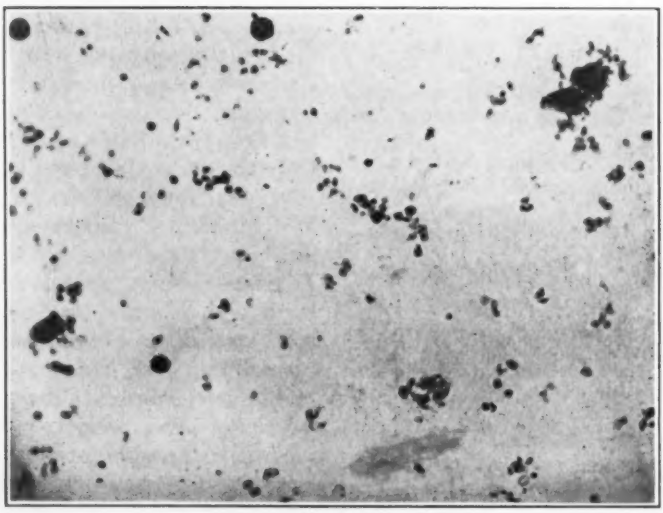
TABLE 1.—AGGLUTINATION OF PLATELETS IN PLATELET-RICH PLASMA OF CASE 1 BY EXPOSURE TO VARIOUS DRUGS FOR 1 HOUR

*Platelet-rich plasma, 1 cc., and 0.1 cc. of the following drugs in physiologic saline solution**	*Percentage of agglutinated platelets in*	
	Case 1 plasma	*Normal plasma*
Quinidine	69.0	0.0
Phenobarbital	3.4	2.8
Priodax	11.4	11.2
Aspirin	1.8	5.0
Demerol	4.4	3.6
Saline control	2.4	1.6

* The final concentration of each drug approximated 10 mg. per 100 cc.



A. Normal platelet-rich plasma



B. Case 1 platelet-rich plasma

FIG. 1.—Wright-stained smears of platelet-rich plasma diluted with 1/10 of its volume of a solution of quinidine in physiologic saline. The final quinidine concentration approximated 10 mg. per 100 cc. X 250.

ment in the proportions of platelets agglutinated, whether of patient or normal control, in the presence of all the drugs save quinidine. With quinidine there were 6 times as many agglutinated platelets in the patient's platelet-rich plasma as in any other sample, either of the patient or of a normal control. A stained preparation (Fig. 1) of these agglutinated platelets showed them to be ragged and partially disintegrated, while the platelets in all other samples were well-defined and intact.

Six months after these observations, the patient's platelet count (direct) was 195,000 per c.mm., and she was asymptomatic. On this occasion no quinidine-induced platelet agglutination could be demonstrated with any combination of the patient's plasma or platelets.

Case 2. A 63-year old woman with angina pectoris, who had taken quinidine without event 1 year previously, resumed this medication in April, 1951. Three days later a trivial laceration bled excessively, and on the sixth day hematuria and purpura appeared. Following admission to another hospital, quinidine was omitted and 1 transfusion was given. The patient continued to take her usual amounts of digitalis and nitroglycerine. The bleeding-time exceeded 1 hour.

We first examined the patient on the third hospital day, at which time active bleeding had ceased, the capillary fragility was but little increased, and the platelet count (direct) was 34,000 per c.mm. The sternal marrow aspirate was normal. The bleeding-time was not tested. A patch test using a tablet of quinidine moistened with saline was negative after 10 hours. Without specific therapy the patient continued rapidly to improve, and successive platelet counts (direct) were: on the sixth hospital day, 115,000; on the ninth hospital day, 292,000; and on the twelfth hospital day, 418,000 per c. mm.

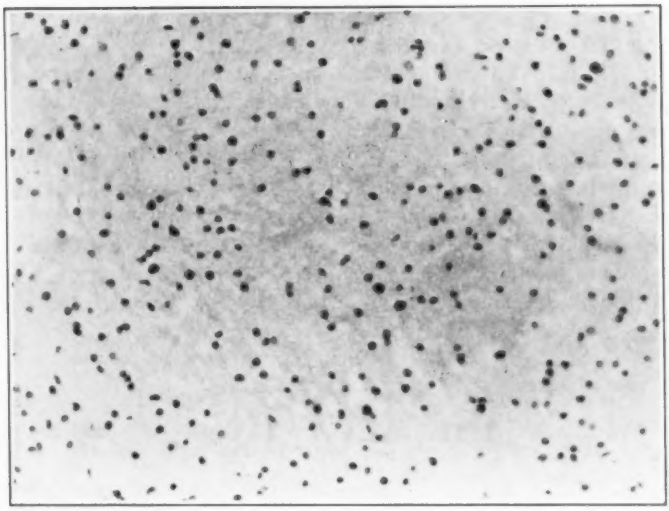
Observations of Platelet Agglutination in Case 2. A variety of studies were done in the attempt to discover the mechanism of the thrombocytopenia. On the sixth hospital day, the patient's platelet-rich plasma was contrasted with that of a normal control in the presence of quinidine in the same manner as in Case 1, but omitting silicone coated glassware. The results, which are presented in Table 2, indicate a strong agglutination of the patient's platelets in her own plasma by quinidine. The same procedure was repeated with a similar outcome on the twelfth hospital day, with the results shown in Figure 2.

TABLE 2.—AGGLUTINATION OF PLATELETS IN PLATELET-RICH PLASMA OF CASE 2 BY EXPOSURE TO QUINIDINE FOR 1 HOUR

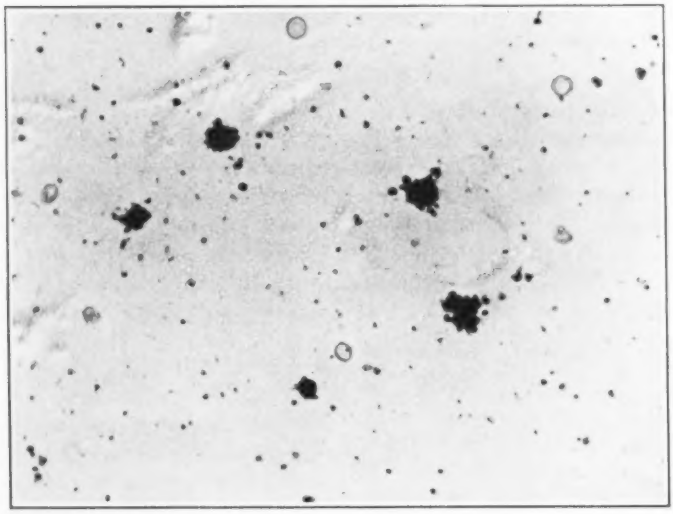
Platelet-rich plasma, 1 cc.	*Solution added, 0.1 cc.*	*Percentage of agglutinated platelets in plasma obtained*	
		6th hospital day	*12th hospital day*
Case 2	Physiologic saline	1.8	0.0
Normal	Physiologic saline	0.6	0.0
Case 2	Quinidine* in physiologic saline	61.0	17.0
Normal	Quinidine* in physiologic saline	5.6	0.0

* The final concentration of quinidine approximated 10 mg. per 100 cc.

In order to discover whether the platelet agglutination was due to a plasma factor active against normal platelets, a sample of plasma obtained on the third hospital day was centrifuged at 22,000 g for 30 minutes. This reduced the platelet count to less than 500 per c.mm. (platelet-poor plasma). After storage for 23 days at −20°C. this platelet-poor plasma was thawed and mixed in equal portions with normal platelet-rich plasma; quinidine was



A. Normal platelet-rich plasma



B. Case 2 platelet-rich plasma

FIG. 2.—Wright-stained smears of platelet-rich plasma diluted with 1/10 of its volume of a solution of quinidine in physiologic saline. The final quinidine concentration approximated 10 mg. per 100 cc. X 250.

then added in the fashion described in the report of Case 1. After shaking for 1 hour at room temperature, the several platelet suspensions were introduced into counting chambers, which were sealed with paraffin and left overnight in the refrigerator. After approximately 18 hours, the number of platelet clumps, as well as of individual platelets, was noted. The result of this study is shown in Table 3, where it may be seen that normal platelets were caused to agglutinate markedly in the presence of the patient's platelet-poor plasma and quinidine but not otherwise. In addition, the concentration of normal platelets was much reduced in the presence of the patient's plasma and quinidine. A repetition of this study, using the same sample of the patient's plasma after storage for 40 days at —20°C., yielded the same result.

TABLE 3.—AGGLUTINATION OF NORMAL PLATELETS BY THE PLATELET-POOR PLASMA OF CASE 2 ON EXPOSURE TO QUINIDINE FOR 1 HOUR

Platelet-rich plasma, 0.5 cc.	*Platelet-poor plasma added 0.5 cc.*	*Solution added, 0.1 cc.*	*Number per c. mm.*	
			Platelet clumps	*Individual platelets*
Normal	Normal	Physiologic saline	15	251,000
Normal	Normal	Quinidine* in physiologic saline	6	271,000
Normal	Case 2	Physiologic saline	7	253,000
Normal	Case 2	Quinidine* in physiologic saline	124	130,000

* The final concentration of quinidine approximated 10 mg. per 100 cc.

A sample of platelet-poor plasma secured from the patient 39 days after the onset of purpura no longer caused agglutination of normal platelets in the presence of quinidine. At the same time, the patient's platelet-rich plasma showed no platelet agglutination on adding this drug.

Two attempts to cause the agglutination of saline suspensions of washed normal platelets by the patient's platelet-poor plasma and quinidine were unsuccessful, using samples taken on the third and ninth hospital days. The reason for failure is inapparent since, as shown in Table 3, the patient's plasma of the third day agglutinated normal platelets in normal plasma, while on the twelfth day (Table 2) the patient's platelets were readily agglutinated in her own plasma by quinidine. We likewise failed to induce agglutination of normal platelets in normal plasma by addition of the patient's serum and quinidine. The serum was obtained on the third hospital day, stored at —20°C., and tested 38 days later.

Discussion. It is unfortunate that practical considerations prevented administration of test doses of quinidine to these patients after their recovery from thrombocytopenia. Nevertheless, there can be little doubt that quinidine was the cause of their purpura. The part played by ACTH in the recovery of Case 1 is uncertain, since quinidine-induced purpura is reported to disappear in approximately 1 week in any event. The observation of apparently inactive megakaryocytes is difficult of interpretation and, if significant, might indicate either depression or exhaustion.

In both Case 1 and Case 2, quinidine effected agglutination of patients' platelets in their own plasmas, and in Case 2 it caused also agglutination of normal platelets in the patient's

plasma. The essential factor thus appeared to reside in the plasma. It persisted for at least 12 days after onset of purpura in the plasma of Case 2, but was absent after 39 days. It could no longer be demonstrated in Case 1 after 6 months. The factor survived storage at –20°C. for at least 40 days in Case 2.

That platelet-lysis accompanies or follows quinidine-induced platelet agglutination in these patients is suggested by the appearance of the platelets in the stained smears in Case 1, and by the *in vitro* reduction of platelet count in Case 2. This point would, however, require further study before a firm conclusion could be reached.

Thus, the thrombocytopenias induced by sedormid[1] and by quinidine are both associated with an abnormal plasma factor which causes platelet agglutination in the presence of the specific drug. This in turn probably leads to platelet lysis. It is reasonable to suspect that this is a mechanism common to many drug-induced thrombocytopenias, except those associated with general marrow aplasia and decrease in all formed blood elements. The methods presented in this report may prove of practical utility in the prompt identification of the offending substance in cases of thrombocytopenic purpura suspected of being drug-induced.

Summary and Conclusions. In 2 instances of thrombocytopenic purpura associated with ingestion of quinidine, agglutination of the patients' platelets was induced by the addition of this drug to platelet-rich plasma. In Case 2 an abnormal factor in the patient's platelet-poor plasma also caused agglutination of normal platelets in the presence of quinidine. The abnormal factor persisted in the plasma of Case 2 for 12 days after onset of purpura, but was absent after 39 days. It withstood storage at —20°C. for at least 40 days.

These observations appear to confirm for quinidine the mechanism of platelet agglutination described by Ackroyd in studies of patients with thrombocytopenia due to sedormid.

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THE USE OF AMPHETAMINE IN BARBITURATE POISONING

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During the past few years there has been a progressive increase in the number of barbiturate deaths and poisonings. In New York City there were 197 deaths in 1945 as contrasted with only 42 deaths in 1939[1]. It is surprising, in view of the considerable clinical experience gained during the past decade, that no definite decision has been reached as to the optimum management of barbiturate poisoning. Too many deaths still occur from overdoses of barbiturates which, in our opinion, could have been averted with the proper utilization of present-day knowledge.

The use of respiratory stimulants or analeptics such as picrotoxin, Metrazol®, Coramine® or Alpha Lobeline® has been attended with some success in treating barbiturate poisoning. Picrotoxin has been advocated by many investigators as the ideal analeptic for barbiturate poisoning. It is now realized, however, that with too vigorous or too frequent use of large doses of picrotoxin, convulsions and a rapidly developing irreversible secondary depression may be produced, thus outweighing its beneficial action. A further objection to the use of picrotoxin, not generally appreciated, is that its latent time of action may be as long as 10 to 30 minutes after intravenous injection.

Metrazol® while less potent than picrotoxin produces immediate effects but has a brief duration of action. The Council on Pharmacy and Chemistry of the American Medical Association sums up its usefulness in barbiturate poisoning with the statement, "Metrazol has not been uniformly effective against large doses of the longer-acting barbiturates, although some case reports of successful results have appeared. The failure of the drug as an analeptic is too often associated with the use of inadequate initial doses and neglect to repeat as often as needed." That Metrazol® should be given further and more extensive clinical trial is suggested by the recent report by Warren, Dooley, and Murphy[9] who found this drug of value in the treatment of 29 cases of barbiturate poisoning.

Riishede[7] of Denmark found nikethamide (Coramine®) inferior to amphetamine (Benzedrine®) in the treatment of acute barbiturate poisoning. Another analeptic, Alpha Lobeline®, frequently exerts a decided but brief stimulant effect on respiration acting via the carotid body reflex, but its effects are uncertain and usually followed by a period of depression due to a nicotine-like reaction. Sodium succinate has not been used sufficiently in barbiturate poisoning to draw any conclusions as to its relative value.

Because of the many difficulties encountered in using the analeptic drugs successfully, some clinicians claim that the great majority of patients poisoned by barbiturates will do better if analeptics are withheld and the emphasis placed on proper supportive treatment and good nursing care[6,8]. Somewhere between the two extremes of all or no analeptic therapy should lie a practical and successful regimen, using the analeptics properly as adjuncts to maintain

the patient's respiratory function until the barbiturate has been excreted and the patient has recovered. In this paper a plan of treatment is offered using injectable amphetamine (Benzedrine®)* which, we feel, is the agent of choice for routine use in the hands of the clinician.

AMPHETAMINE. Myerson[5], on the basis of experimental studies, first suggested the use of amphetamine in barbiturate poisoning in 1939. However, it was not until 1946 that the first clinical paper on its use in barbiturate poisoning was published by Freireich and Landsberg[2]. Recently, Riishede[7] compared the treatment of 132 patients with barbiturate poisoning given amphetamine with 61 cases given nikethamide (Coramine®). Of the 61 patients treated with nikethamide, 44% died, while only 6% of the 132 given amphetamine died. The fact that large doses of amphetamine may be given intravenously without harm to the patient has been well demonstrated[3,4,7].

Management of Barbiturate Poisoned Patients. (a) EVALUATION OF DEGREE OF POISONING. The patient acutely poisoned by an overdose of a barbiturate is usually comatose, the depth of central nervous system depression being determined by the amount of drug taken and the duration of its action. As well known, the overdoses of the so-called short-acting barbiturates such as seco-barbital (Seconal®), pentobarbital (Nembutal®), vinbarbital (Delvinal®), and amobarbital (Amytal®) rapidly depress the patient to profound coma in about 30 minutes. If untreated, death may occur in 1 or 2 hours. With the slower-acting compounds such as barbital and phenobarbital, the depression comes on more slowly and lasts much longer; although it is never as profound as that seen with the short-acting barbiturates.

The severely poisoned patient shows a weak and rapid pulse with a low systolic pressure. Cardiac action is weak due to direct myocardial depression by the drug, while the heart may be reflexly accelerated. The pupils are generally fixed and small and there is no corneal reflex. Respirations are shallow and slow because of a depression of respiratory centers in the medulla. Deep spinal reflexes are usually absent, but rarely may be hyperactive; a positive Babinski is often present. The peripheral circulatory collapse often seen is due to direct action of the drug on the smooth muscle of the arteriolar wall.

Watts and Ruthberg[10] have pointed out that previous observers have made little attempt to evaluate quantitatively the depth of narcosis produced by the barbiturate. They believe that such an evaluation serves as a valuable guide in outlining restorative therapy and judging its effectiveness. Accordingly, these workers devised a classification of the depth of narcosis consisting of 4 grades (Table 1). They felt that the most important point of clinical evaluation lay between grades 3 and 4 which is differentiated by the presence or the loss of the corneal reflex. The application of this classification to the eleven cases we have reported (Table 2) soon revealed considerable discrepancy between the depth of narcosis noted and the rate of recovery for those patients placed in grade 4. For this reason, we have added a fifth grade with the main differentiating points being the presence or absence of shock and/or respiratory arrest. We have used this revised classification as a guide in the selection of appropriate restorative therapy and for estimating the dose and frequency of administration of amphetamine required for each individual.

(b) TREATMENT PROCEDURE. Our routine of treatment was as follows:

1. Provide adequate airway if tracheal obstruction is present with continuous oxygen and frequent aspiration of secretions. Provide positive pressure oxygen when pulmonary edema is present.

2. Treatment of shock with plasma or whole blood.

3. Give amphetamine as indicated in proper dosage and frequency.

4. Gastric lavage if the patient had taken the drug within two hours of admission. (Too much emphasis is frequently placed on this procedure and valuable time may be lost when the preceding procedures should have been instituted. Furthermore, in the uncon-

* Amphetamine (Benzedrine Sulfate®), Smith, Kline and French, is available in 2 cc. ampules containing 20 mg/cc.

Amphetamine (Monetamine Sulfate®), Northwest Laboratories, is now available in a 10 cc. sterile vial containing 40 mg/cc.

scious patient there is danger of aspiration of fluids.)

5. Adequate hydration with intravenous fluids.

6. Penicillin by intramuscular injection.

7. Indwelling urethral catheter.

8. Frequent observation by nursing staff for signs of increasing coma.

The dosage schedule for intravenous amphetamine used was first guided by the experiences of Freireich and Lansberg[2]. They gave 40 mg. of amphetamine intravenously as an initial dose, followed by 20 mg. every ½ hour. It soon became evident to us that larger doses could be given safely and more effectively so that doses up to 100 mg. every ½ hour to 1 hour were administered, being careful to base this medication on close clinical observation.

Case Reports.* The 11 cases of barbiturate poisoning treated with amphetamine are listed in chronological order in Table 2. Since in most of these cases other analeptics besides amphetamine were employed, a precise evaluation of the value of the latter drug is impossible but some indication of its comparative effectiveness can be gained.

Case 5, a 32-year old woman who had taken 50 grains of Delvinal® 2 hours prior to admission. Immediately upon entering the emergency treatment room she was given 4 mg. of picrotoxin intravenously. Ten minutes later she ceased breathing while an attempt was being made to pass a Levine tube. The patient was immediately given oxygen by mask and artificial respiration. Fifteen minutes after picrotoxin she was given 5 cc. of Coramine® and 40 mg. of amphetamine intravenously. Very shortly afterwards the patient resumed normal breathing. An intratracheal tube was then inserted and injections of amphetamine, in from 10 to 20

TABLE 1.—CLASSIFICATION OF DEPTH OF NARCOSIS IN BARBITURATE POISONING

Grade	*Conscious*	*Tendon Reflex*	*Corneal Reflex*	*Swallow Reflex*	*Pupils*	*Coma*	*Shock*	*Resp. Arrest*
1	Yes	Yes	Yes	Yes	Normal	No	No	No
2	Semi	Yes	Yes	Yes	Constric.	No	No	No
3	No	Absent	Yes	Absent	Pinpoint	Yes	No	No
4	No	Absent	Absent*	Absent	Pinpoint	Deep	No	No
5	No	Absent	Absent	Absent	Pinpoint	Deep	Yes*	Yes*

* The most important differential of a grade 3 from a grade 4 is the loss of the corneal reflex and between 4 and 5, the presence of shock or respiratory arrest.

TABLE 2.—CASES OF BARBITURATE POISONING TREATED WITH AMPHETAMINE

Case	*Sex*	*Age*	*Type and Amount of Barbiturate*	*Hours Unconscious Before* R	*Grade*	*Amount of Amphetamine*	*Time to Regain Consciousness*
1	F	70	?	?	4	60 mg.	6 hours
2	F	77	?	?	4	120 mg.	7 hours
3	F	20	?	?	4	40 mg.	6 hours
4	F	30	Tuinal 25½ grs.	?	4	110 mg.	11 hours
5	F	32	Delvinal Sodium 50 grs.	2 hours	5	120 mg.	12 hrs. (pain. stim.) 26 hours
6	F	54	Luminal 75 grs.	8 hours+	4	360 mg. 700 mg.	37 hrs. (pain. stim.) 4 days
7	F	29	Nembutal 16½ grs. and alcohol	5 hours+	4	120 mg.	2 hrs. (pain. stim.) 9 hours
8	F	54	Tuinal 30 grs.	1½ hours	4	160 mg.	6½ hrs. (pain. stim.) 9 hours
9	F	42	?	1 hour	4	280 mg.	2½ hrs. (pain. stim.) 10½ hours
10	M	40	Seconal 30+ grs.	4 hours	4	320 mg.	15 hrs. (pain. stim.)
11	F	37	Seconal 50 grs.	1 hour	5	60 mg.	5½ hrs. (pain. stim.) 10 hours

* Clinical material was obtained from Lenox Hill Hospital, New York, N. Y.; Good Samaritan Hospital and Providence Hospital, Portland, Oregon.

mg. doses continued at about 2-hour intervals. The patient reacted to painful stimulation in 12 hours and was fully conscious in 26 hours. A total of 120 mg. of amphetamine had been used.

CASE 6, a 54-year old woman who had ingested about 75 grains of phenobarbital, a long-acting barbiturate, 8 or more hours prior to admission. While unconscious, this large dose of phenobarbital did not produce any marked effect on the respiratory center or any signs of shock. Amphetamine was given in doses varying from 20 mg. to 60 mg. at hourly intervals according to the clinical condition of the patient. There were at times periods of 3 to 4 hours when no medication was given to the patient. It is now felt that the patient's return to consciousness would have been more prompt had the drug been given more energetically.

CASE 4, a 30-year old woman took 25½ grains of Tuinal®, 2 hours prior to admission. On admission she received 30 mg. of amphetamine intravenously and 20 mg. every hour for 4 doses. A total of 110 mg. of amphetamine restored her to consciousness in 11 hours.

CASE 8, a 54-year old female took 30 grains of Tuinal® 1½ hours before admission. She was cyanotic and her blood pressure was 96/60 mm. Hg. A total of 160 mg. of amphetamine was used to restore her to consciousness in 9 hours.

CASE 10, a 40-year old male took at least 30 grains of Seconal®. Except for an injection of 3 mg. of picrotoxin and 2 injections of caffeine sodium benzoate, amphetamine was the major analeptic used. While this patient reacted to painful stimulation in 15 hours after a total of 320 mg. of amphetamine had been given, the patient's physician then resorted to picrotoxin. Had larger doses of amphetamine been continued, the patient undoubtedly would have been restored to consciousness earlier.

CASE 11, a 37-year old woman ingested 50 grains of Seconal® 1 hour prior to admission. She was comatose, cyanotic and in shock on admission. Pupils were dilated and the corneal reflex was absent. Gastric lavage was performed immediately, and continuous oxygen given. The patient was given 2 cc. of caffeine and sodium benzoate and 20 mg. of amphetamine intravenously. Her blood pressure rose from an imperceptible level to 175/110. Two and one-half hours later her blood pressure fell to 80/60. She was then given 40 mg. of amphetamine and her blood pressure rose to 170/100. Five and one-half hours later there was response to painful stimulation and full consciousness returned in 10 hours.

Patients 1, 2, 3, and 7 listed in Table 2 would probably have lived had no analeptic been employed and with only conservative symptomatic therapy. In patient 5 amphetamine was considered definitely life-saving; this case illustrates several important factors in the treatment of barbiturate poisoning. First, the short-acting barbiturates produce the most profound and rapid effect on the patient. Secondly, the use of picrotoxin in this patient failed to influence the profound depression at a critical time due to its lag in effect. Also, time was wasted on gastric lavage which might have been better spent on other more important procedures.

Case 6, in contrast to Case 5, had taken a larger dose of drug, yet 75 grains of phenobarbital 8 hours after ingestion produced very little depression of respiration or any serious signs of shock; quite different was the effect on only 30 grains of Delvinal® in patient 5. In patient 6 amphetamine may have been life-saving through its effect of shortening the period of unconsciousness and thereby reducing the chances of pulmonary complications developing.

Cases 4 and 8 illustrate the fact that approximately the same dose of a barbiturate, in this case Tuinal®, may have a much more severe effect on 1 individual than another.

Discussion. Early reports of the treatment of barbiturate poisoning with amphetamine were criticised because the patients treated were not severely poisoned and the number of patients reported was small. In a series of 160 cases collected from the literature[2,3,4,7] with the addition of 11 cases presented in this series, we find that 30 patients could be classified as grade 5. Of these, 14 died. Since all of these patients

would have died in respiratory arrest and/or circulatory collapse, we feel that the 16 patients who lived showed that amphetamine is capable of counteracting the toxic effects of severe barbiturate poisoning. It must be remembered, however, that even among grade 4 patients there are a large number of deaths resulting from such complications as pneumonia and atelectasis. Any factor decreasing the period of coma should reduce the number of these secondary complications.

We feel that such restoratives or stimulants as the analeptic drugs should be used in treating all severe cases of barbiturate poisoning. Amphetamine appears to be the analeptic of choice since it has a fairly large safety factor and is promptly effective if used in sufficiently large doses given repeatedly.

Summary. Eleven cases of barbiturate poisoning treated successfully with amphetamine as the major analeptic drug used have been described. There were no deaths in this small series even though 2 patients were first seen in a state of respiratory arrest and circulatory collapse. Our experience with amphetamine confirms the favorable results presented in 160 cases summarized in the literature. It is striking to note that even with very large doses of amphetamine no convulsions could be elicited. Thus amphetamine because of its safety appears to be the ideal analeptic combined with rational supportive therapy in the treatment of severe barbiturate poisoning.

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HYPERTENSION AS A REACTION PATTERN TO STRESS. CORRELATION OF CIRCULATORY HEMODYNAMICS WITH CHANGES IN THE ATTITUDE AND EMOTIONAL STATE‡

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It has been repeatedly shown that significant elevations of blood pressure occur in many individuals as part of their pattern of reaction to stressful life experiences. There is some evidence that such a mechanism may be pertinent to the pathophysiology involved in essential hypertension[7,13]. Since elevations in blood pressure may be attributable either to an increase in peripheral resistance or to an increase in cardiac output, a study was made of the relationship between life situations, emotions, and variations in hemodynamics with special reference to factors underlying changes in arterial pressure.

Material and Methods. Thirty patients who habitually showed a systolic blood pressure over 150 mm. and a diastolic blood pressure of 90 mm. Hg or more were selected from the clinics of the New York Hospital. These were compared with a group of 16 other patients without hypertension, and 28 normotensive subjects without complaints. Significant findings derived from physical examination and appropriate laboratory tests were recorded in each case. Data concerning the personality of each subject were derived from interviews with the patient and other members of his family, from associations, analysis of dream material and psychological tests. A further appraisal of attitudes and motivations of each subject was made by observation of his reactions especially during discussion of difficult life experiences, by things said and left unsaid, by gestures, slips of the tongue, blocking, projections and other indications in his behavior and stream of talk. These data were then correlated with the symptoms and with the measurements of circulatory functions. At each visit the arterial pressure in the arm was ascertained by the auscultatory method. From time to time, measurements of cardiac output and peripheral resistance were also made, using the critically damped ballistocardiograph of Nickerson[5]. While this instrument may not be suitable for comparative determinations of cardiac output from individual to individual, it can reliably reflect relative differences in cardiac output in the same individual subject, especially when he is observed more or less continuously in a single experiment. The values for stroke volume and cardiac index

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were calculated from the formula of Nickerson *et al.*[6]. The mean blood pressure was determined by adding one third of the pulse pressure to the diastolic pressure. The peripheral resistance was derived by dividing the cardiac index into the mean pressure. Most of the tests were performed in the morning after a night's sleep and without breakfast. A few were performed at other times of the day, but not less than 2 hours after the last meal, and after at least 20 minutes' rest spent partly on a bed and partly on the ballistocardiographic table.

In 20 of the patients with hypertension the hemodynamic response to a standard exercise was measured. The exercise used was that devised by Master, which is adjusted for age, sex and weight of the subject[4]. The results are compared with the response to exercise of 28 normotensive controls.

In 21 patients with hypertension the hemodynamic response during a probing interview was studied and compared with the response of 16 non-hypertensive patients during a similar interview. In 2 of the hypertensive patients measurements were also made during the interview of renal blood flow and glomerular filtration rate by the para-amino hippuric acid and inulin clearance methods of Homer Smith[9]. The conscious and unconscious emotional state of each subject at the time of the test and the effects of the current situation were appraised from verbal and other responses, both spontaneous and in answer to questions. Special note was made of cutaneous, vascular and respiratory changes, sweating, restlessness, dryness of the mouth and the behavior of the subject toward the physician. During control periods, an effort was made to keep the circumstances of the experiment as neutral as possible and the subject lightly diverted. Following suitable control periods a probing discussion was undertaken of the patient's pertinent personal conflicts after which there was a second control period in which the subject was strongly reassured and diverted. When feasible, the experiments were later reviewed with the patient and reevaluated in the light of recollections, associations, and pertinent dreams.

Results. 1. RESPONSE OF HYPERTENSIVE AND NON-HYPERTENSIVE SUBJECTS TO EXERCISE UNDER RELATIVELY NEUTRAL CIRCUMSTANCES. Measurements at rest and following exercise in 20 hypertensives and 28 healthy non-hypertensive subjects are given in Table 1, and graphically in Fig. 1. The response to exercise as judged by the heart rate and by the return of heart rate and cardiac index to resting values was essentially similar in the two groups. There was uniformly observed a sharp rise in stroke volume and cardiac output associated with a fall in peripheral resistance following exercise performed in the absence of significant emotional conflict.

COMMENT. These results confirm those of Taylor *et al.*[11] by demonstrating the failure of exercise to elevate blood pressure more in hypertensive than in non-hypertensive subjects. They do not support the idea that exercise is a form of stress unfavorable to the hypertensive process, a notion which is often implied in the frequent restrictions placed on those subjects with respect to exercise.

2. RESPONSE OF HYPERTENSIVE AND NON-HYPERTENSIVE SUBJECTS TO EXERCISE DURING MANIFEST ANXIETY. It was shown in an earlier publication that when normotensive subjects happened to be exercised during a period of overt anxiety the increase in heart rate and cardiac index was greater than when the same exercise was performed during periods of relaxation, and there was delay in the return of these values to the resting levels[10]. Among the hypertensive and non-hypertensive subjects of the present study, essentially the same pattern of response was observed. Typical responses of a hypertensive to exercise during a period of manifest anxiety and during one of apparent relaxation are seen in Fig. 2 which gives graphically the results obtained in a 48-year old female with hypertension of several years' duration. Although her heart was apparently normal she was fearful of the exercise on the day of the first test and was uneasy about the results of the test. In addition, she was aware of anxiety about

TABLE 1.—CARDIOVASCULAR CHANGES FOLLOWING EXERCISE IN HYPERTENSION. CIRCULATORY MEASUREMENTS BEFORE AND AFTER A STANDARD EXERCISE TEST IN A GROUP OF 20 SUBJECTS WITH HYPERTENSION AND 28 SUBJECTS WITHOUT HYPERTENSION OR OTHER DISEASE. THE BLOOD PRESSURE AND PERIPHERAL RESISTANCE ARE HIGHER AND THE CARDIAC OUTPUT SOMEWHAT LOWER IN THE HYPERTENSIVE GROUP THAN IN THE NORMOTENSIVE GROUP, BUT THERE IS NO SIGNIFICANT DIFFERENCE IN THE RESPONSE TO EXERCISE OF THE TWO GROUPS. ABBREVIATIONS: Sv. = STROKE VOLUME; C.I. = CARDIAC INDEX; P.R. = PERIPHERAL RESISTANCE.

HYPERTENSIVE PATIENTS

Patient	Sex & Age	Resting					2′ After Exercise					3′ After Exercise					5′ After Exercise					10′ After Exercise				
		B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.
1	M-59	158/90	57	69	2.3	50	164/84	63	63	2.3	49	161/82	62	72	2.6	34	158/85	64	70	2.6	43	154/93	62	62	2.2	42
2	M-55	143/92	63	70	2.2	51	157/88	68	78	2.6	42	147/88	67	89	2.9	37	139/85	65	66	2.1	49	134/87	64	56	1.8	58
3	M-43	198/138	65	53	1.6	97	212/125	69	73	2.4	64	202/125	67	65	2.1	73	191/122	66	64	2.0	72	185/122	72	39	1.4	106
4	M-36	153/103	74	80	3.0	40	161/101	76	116	4.5	27	162/97	73	98	3.6	33	157/101	70	89	3.2	38	147/98	70	86	3.1	38
5	M-31	135/97	80	94	4.0	28	150/99	73	115	4.4	26	142/93	77	104	4.2	26	140/98	81	93	4.0	28	136/91	80	70	3.0	35
6	M-36	202/152	84	38	1.7	100	227/145	97	71	3.6	48	206/152	82	50	2.1	81	196/144	82	37	1.6	100	198/150	82	35	1.5	111
7	M-31	164/118	60	61	2.1	64	169/117	72	80	3.3	41	167/118	70	78	3.1	43	169/119	66	71	2.7	51	168/118	65	67	2.5	55
8	M-40	150/96	75	63	2.5	46	157/95	68	74	2.6	45	154/97	80	65	2.7	43	151/96	71	60	2.2	52	156/102	78	42	1.7	71
9	M-49	182/108	96	46	2.5	55	196/126	100	68	3.8	40	186/128	104	50	2.9	51	175/126	106	55	3.2	44	156/116	101	45	2.5	52
10	M-31	161/107	57	87	2.9	43	173/98	58	79	2.7	45	172/101	54	77	2.5	51	166/104	63	51	1.9	66	165/109	54	110	3.5	36
11	F-53	157/102	86	80	4.0	30	163/98	95	127	7.0	17	160/96	92	108	5.8	20	151/91	92	100	5.4	21	150/100	88	92	4.7	25
12	F-37	166/96	65	69	2.8	43	184/98	72	98	4.4	29	174/98	72	107	4.8	26	169/99	70	93	4.1	30	179/105	69	80	3.5	36
13	F-39	236/144	67	61	2.2	80	245/150	71	85	3.2	57	239/148	70	58	2.2	83	234/154	79	62	2.6	70	232/148	72	51	1.9	91
14	F-61	204/94	60	105	3.6	36	238/100	70	102	4.1	36	—	—	—	—	—	229/102	65	105	3.9	37	215/100	64	96	3.5	39
15	F-44	193/124	80	73	3.7	39.3	196/117	92	95	5.6	25	—	—	—	—	—	189/123	82	79	4.1	36	199/127	83	70	3.7	41
16	F-58	173/96	62	61	2.4	51	182/90	69	84	3.8	32	173/90	66	72	3.1	38	167/89	67	66	2.9	40	163/94	66	50	2.1	56
17	F-48	160/107	72	41	1.9	66	169/112	76	53	2.6	51	163/110	74	68	3.2	40	159/109	70	43	2.0	65	158/105	66	46	1.9	63
18	F-51	191/114	68	63	2.6	53	202/110	70	85	3.6	39	188/111	72	85	3.8	37	189/110	69	78	3.3	41	183/110	65	73	2.9	46
19	F-52	194/115	66	50	2.1	67	215/111	66	84	3.5	42	207/109	68	71	3.0	47	119/112	68	71	3.0	47	203/122	64	63	2.5	99
20	F-43	171/104	87	78	4.1	31	202/98	89	112	6.2	21	202/96	88	102	5.5	24	194/98	82	101	5.1	26	188/102	86	86	4.5	29

NON-HYPERTENSIVE PATIENTS

Patient	Sex & Age	Resting					2' After Exercise					3' After Exercise					5' After Exercise					10' After Exercise				
		B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.
1	M-29	106/67	58	113	3.3	25	117/63	59	132	3.8	21	111/62	57	140	3.9	20	109/60	58	124	3.6	22	106/61	62	116	3.6	21
2	M-32	105/68	82	86	3.5	23	114/70	77	121	4.7	18	111/70	78	117	4.6	18	106/69	83	100	8.3	20	104/71	82	89	3.7	22
3	M-34	112/75	77	84	3.2	27	116/73	73	110	4.0	22	114/71	76	77	2.9	29	110/73	76	76	2.9	30	110/72	73	79	2.8	30
4	M-32	115/63	60	97	3.3	24	132/66	62	116	4.0	22	124/66	62	107	3.8	23	116/65	61	100	3.4	24	114/67	60	97	3.3	25
5	M-29	94/59	59	84	2.7	27	110/59	58	97	3.0	25	108/58	56	96	2.9	26	106/58	60	94	3.0	25	95/60	59	85	2.7	27
6	M-24	100/58	64	81	2.6	28	110/59	64	99	3.2	24	107/60	63	99	3.1	25	103/61	59	90	2.6	28	101/61	62	79	2.4	31
7	M-21	120/71	60	90	2.4	36	95/52	59	89	2.4	28	91/51	61	91	2.5	26	93/51	59	91	2.4	27	111/69	58	94	2.5	33
8	M-34	112/70	73	109	4.5	19	120/72	82	139	6.4	14.0	116/68	76	143	6.1	14	115/68	73	121	5.0	17	108/68	74	96	4.0	24
9	M-32	109/60	68	127	4.3	18	126/61	58	178	5.2	16	121/67	57	176	5.0	17	120/65	63	147	4.6	18	111/67	61	134	4.1	24
10	M-31	108/64	50	104	2.7	29	115/64	51	117	3.1	26	113/61	53	115	3.2	25	112/59	50	114	3.0	26	106/60	50	103	2.7	28
11	M-29	137/79	89	95	4.7	21	149/71	109	120	7.2	13	139/73	104	114	7.1	13	129/71	91	105	5.3	17	121/79	90	88	4.4	21
12	M-30	110/63	60	104	3.1	26	116/59	66	136	4.4	18	114/62	63	128	4.0	20	116/61	63	129	4.0	20	109/65	62	109	3.3	24
13	M-42	118/74	56	128	3.7	24	119/71	54	130	3.7	24	118/69	54	127	3.6	24	116/66	53	125	3.4	24	114/71	57	108	3.2	27
14	M-30	102/67	72	67	2.7	29	121/65	67	81	3.0	28	113/64	67	75	2.8	32	110/65	71	70	2.8	29	108/67	70	67	2.6	31
15	M-29	134/65	82	93	3.8	33	157/61	88	125	5.5	17	152/63	86	113	4.8	19	149/60	83	95	3.9	23	133/68	88	65	2.8	32
16	M-22	106/60	50	90	2.4	31	116/57	50	95	2.5	30	114/60	50	84	2.3	35	112/63	50	82	2.2	36	109/61	53	76	2.2	36
17	F-21	106/59	77	59	2.9	26	127/62	82	93	4.9	17	117/58	77	77	3.8	21	113/58	78	71	3.5	22	105/59	78	65	3.2	23
18	F-22	94/62	55	56	1.9	38	106/57	57	78	2.8	27	101/61	53	71	2.3	32	101/62	51	66	2.1	36	99/63	54	58	2.0	39
19	F-20	112/76	78	82	3.4	26	117/75	85	108	4.9	18	112/78	91	113	5.5	16	113/78	85	97	4.4	21	110/79	83	82	3.6	25
20	F-46	108/71	57	56	1.7	48	122/75	60	86	2.8	32	116/72	60	76	2.5	35	106/66	56	65	2.0	40	105/70	64	68	2.3	36
21	F-34	101/60	87	62	3.6	20	113/64	87	93	5.6	14	110/63	86	91	5.3	15	103/58	78	79	4.2	18	101/62	75	62	3.2	24
22	F-22	110/67	66	63	2.4	35	116/65	59	81	2.7	30	113/63	60	76	2.6	31	109/66	61	61	2.1	38	106/70	65	57	2.1	39
23	F-22	99/66	59	60	2.1	36	98/64	68	70	2.9	26	95/62	54	72	2.3	31	94/61	70	68	2.8	25	93/64	64	63	2.4	31
24	F-34	98/64	67	64	2.4	31	109/64	68	88	3.4	23	108/64	72	84	3.4	23	100/59	68	76	2.9	25	99/59	68	70	2.7	27
25	F-23	105/69	67	88	3.6	14	117/62	67	122	5.0	16	109/63	66	112	4.5	17	108/65	74	93	4.1	19	102/68	69	87	3.7	21
26	F-21	114/75	62	98	3.3	27	119/59	72	125	5.0	16	113/59	67	114	4.2	18	111/62	64	108	3.8	21	112/70	67	108	4.0	21
27	F-34	117/68	63	80	3.2	27	125/74	62	105	4.1	22	124/74	63	78	3.1	30	120/72	63	74	2.9	30	119/75	61	75	2.9	30
28	F-32	102/65	68	61	2.5	31	118/67	78	91	4.3	20	113/66	73	92	4.9	20	108/68	74	80	3.6	23	101/67	68	70	2.9	27

certain domestic problems. On the occasion of the second test she was considerably more relaxed, having in the meantime disposed of a number of her problems. In both instances exercise was associated with an increase in heart rate and stroke volume, a decrease in peripheral resistance, and a widening of pulse pressure with little change in mean blood pressure.

3. RESPONSE OF HYPERTENSIVE AND NON-HYPERTENSIVE SUBJECTS DURING INTERVIEWS PRODUCTIVE OF EMOTIONAL CONFLICT. During stressful interviews the hemodynamic response was much less uniform than that observed following exercise. This variability of response has already been described by Hickam *et al.*[3] but the significance of the differences is still unclear. Some sub-

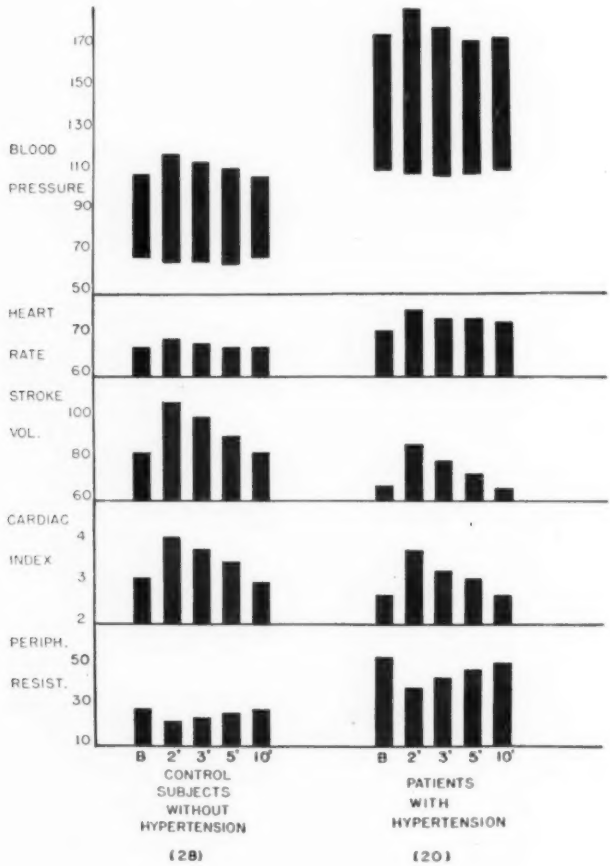

FIG. 1.—*Cardiovascular changes following exercise in hypertension.* Mean values of circulatory measurements before (B) and after (2′, 3′, 5′ and 10′) a standard exercise test in a group of 20 subjects with hypertension and 28 subjects without hypertension or other disease. The blood pressure and peripheral resistance are higher, and the cardiac output somewhat lower in the hypertensive group than in the normotensive group, but there is no significant difference in the response to exercise of the two groups. (Data of Table 1).

jects reacted with an increase in cardiac output and arterial pressure accompanied by a fall in peripheral resistance, a pattern of reaction similar to that induced by exercise. Others showed a rise in blood pressure which was attributable to an increase in peripheral resistance with cardiac output unchanged or actually decreased. Many of the subjects shifted from one pattern to the other or displayed mixed patterns during the interview. Variations in cardiac output were the result of changes in both rate and stroke volume, but in general the stroke volume displayed greater variation than did the pulse rate. Elevation of arterial pressure was uniformly observed during discussion of topics of significant conflict but it was not possible to identify the underlying hemodynamic pattern from the estimation of systolic

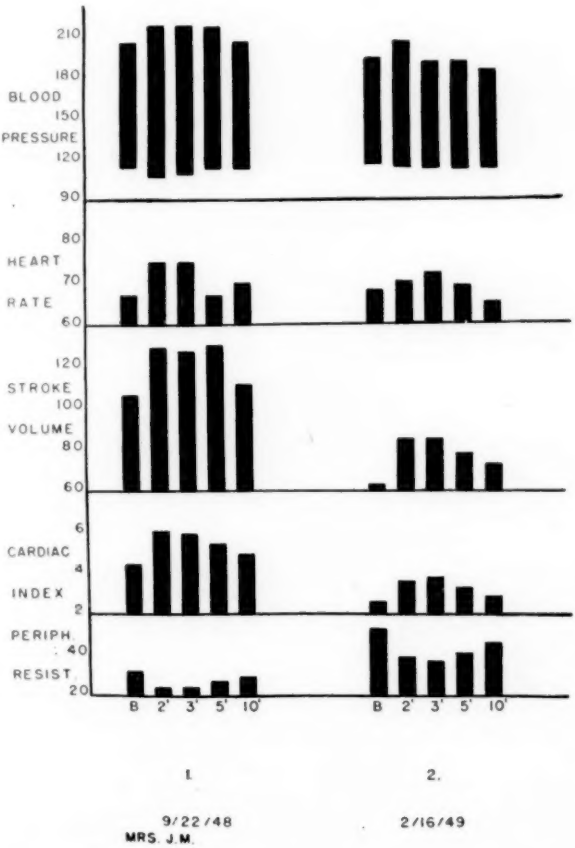

FIG. 2.—*Exercise tolerance in a hypertensive subject during anxiety and relaxation.* Circulatory measurements before (B) and after (2′, 3′, 5′ and 10′) a standard exercise test on two occasions are given. The patient was a 48 year-old woman with complaints of headaches and palpitations. On the occasion of the first test (9/22/48) she exhibited marked anxiety about her own problems and about the outcome of the test. On the second occasion (2/16/49) there was no manifest anxiety. Exercise during relaxation caused a lesser rise in cardiac output than it did during anxiety.

and diastolic pressure alone. The hemodynamic pattern did appear to correlate to some degree, however, with the obviousness of the subject's emotional disturbance. When there was readily evident anxiety or hostility, the "exercise" pattern with increased cardiac output was more often observed. When the manifestations of emotional disturbance changed during the interview, the hemodynamic pattern was also likely to change without the shift being detectable in the curve of arterial pressure. The reactions of 21 hypertensive patients were compared with those of 16 non-hypertensives. The data are summarized in Table 2.

TABLE 2.—CIRCULATORY MEASUREMENTS DURING CONTROL OBSERVATIONS AND DURING STRESSFUL INTERVIEWS IN 16 NORMOTENSIVE AND 21 HYPERTENSIVE SUBJECTS

HYPERTENSIVE PATIENTS

Patient	Sex & Age	Control					Interview				
		B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.
1	F-46	142/94	65	44	1.7	65	158/129	75	34	1.5	93
2	F-61	204/94	60	105	3.6	36	250/112	68	96	3.7	43
3	F-50	191/114	68	63	2.6	53	204/113	67	106	4.4	32
4	F-62	176/89	74	62	3.2	36	197/97	87	70	4.2	31
5	F-39	236/144	67	61	2.2	80	267/163	71	96	3.6	54
6	M-41	130/95	75	111	3.8	28	165/108	96	151	6.5	20
7	M-40	172/105	60	115	3.3	42	170/108	63	89	2.7	48
8	F-43	171/104	87	78	4.1	31	189/95	93	78	4.5	28
9	F-37	138/102	74	42	2.0	58	141/102	84	87	4.6	25
10	M-55	134/87	64	56	1.8	58	162/105	64	96	3.0	41
11	M-36	196/148	79	29	1.3	129	224/172	82	52	2.3	84
12	M-31	135/97	80	94	4.0	28	144/98	78	103	4.3	27
13	F-42	179/109	74	81	3.7	36	215/123	91	91	5.1	30
14	F-42	172/121	76	35	1.5	89	237/148	108	66	4.1	43
15	F-52	194/115	66	50	2.1	67	231/136	70	52	2.3	73
16	M-49	182/108	96	46	2.5	55	201/139	98	62	3.4	47
17	F-37	166/96	65	69	2.8	43	198/120	68	89	3.8	38
18	F-62	170/94	70	62	2.9	40.5	202/103	75	115	5.8	28
19	F-61	158/84	71	36	1.5	73.5	160/109	76	49	2.7	53
20	F-43	174/98	77	33	1.8	68	190/106	84	50	3.2	42

NON-HYPERTENSIVE PATIENTS

Patient	Sex & Age	Control					Interview				
		B.P.	Rate	Sv.	C.I.	P.R.	B.P.	Rate	Sv.	C.I.	P.R.
1	F-32	100/66	75	66	3.4	23	118/70	100	68	4.7	18
2	F-23	100/68	88	63	4.0	20	128/78	99	124	9.9	9.6
3	F-17	116/67	97	100	5.8	14	136/82	124	160	12.0	9.1
4	F-31	108/78	94	60	3.8	23	120/80	95	77	45	21
5	F-48	144/78	76	71	3.8	26	175/88	90	83	5.2	23
6	F-34	111/74	67	62	2.2	40	120/70	89	102	4.8	20
7	F-39	90/56	90	46	2.6	26	116/78	103	56	35	28
8	F-32	110/75	90	45	2.7	33	124/84	102	91	6.1	16
9	F-55	115/81	74	46	2.2	42	111/79	80	88	4.5	20
10	F-45	115/64	56	68	2.7	30	121/66	60	116	4.9	17
11	M-32	124/66	82	140	5.9	14	132/80	90	110	5.1	19
12	M-41	118/79	75	68	2.5	37	127/84	90	100	4.5	22
13	M-48	115/84	88	75	4.1	24	134/78	94	115	6.9	14
14	M-29	127/91	73	88	3.1	33	129/89	77	126	4.6	22
15	M-58	135/84	80	116	4.2	24	151/89	82	132	5.0	22
16	M-47	140/84	58	82	2.7	39	136/84	64	96	3.4	29

CASE 1. Illustrating elevations of blood pressure due to increase in peripheral resistance at one time and increase in cardiac output at another is the case of a 38-year old white male in whom casual blood pressures over a 14 year period had frequently revealed a diastolic pressure of over 100 mm. of mercury. As a child the patient had been very aggressive and quick tempered, and fought frequently with an older brother. The death of a younger sibling, aged 1½ years, when the patient was 5, was "jokingly" attributed by the family to the beatings inflicted on the infant by the patient. At age 12, following the death of the mother, of whom he now has practically no recollection, his outward behavior changed markedly, with the acquisition of a soft spoken manner and calm outward appearance. His hypertension was first noted at age 23 and has fluctuated considerably at and above normal levels since

that time. The patient's father had had angina for several years before his sudden death in 1939. Recently the patient had been told his complaint of diffuse left lower axillary pain indicated the presence of angina pectoris and that an electrocardiogram was indicated. During the experimental observations, while preparations were being made to take an electrocardiogram, the patient's blood pressure rose briskly with an associated sharp increase in peripheral resistance. His hostility toward his parents in which he displayed evident feeling, the blood pressure remained elevated but peripheral resistance fell while cardiac output rose correspondingly.

Other subjects who remained comparatively poised and restrained throughout the stressful portion of the experiment displayed an elevation of blood pressure attributable wholly to a

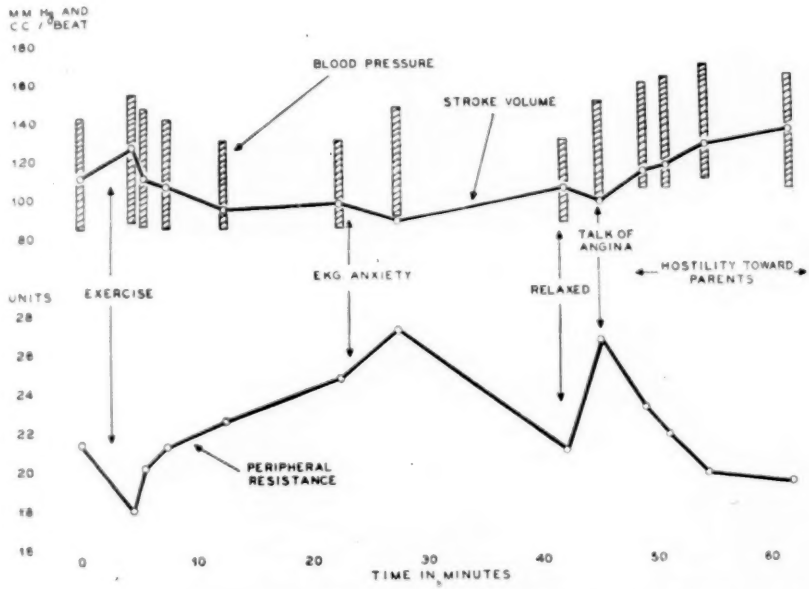

FIG. 3.—*Changes in blood pressure, stroke volume, and peripheral resistance following exercise and during an interview with a hypertensive patient.* (Case 1) Peripheral resistance rose sharply during the two episodes of stress in which the patient's manner was restrained and superficially calm. During an overt expression of hostility, however, peripheral resistance fell as it did following exercise.

manner at this time was tense but poised and compliant. After the electrocardiogram had been taken the patient was reassured and, as he became more relaxed, the blood pressure level fell with an accompanying decrease in peripheral resistance. Later when the topic of angina pectoris was abruptly introduced into the discussion, the blood pressure rose again with a sharp elevation of peripheral resistance. His manner at this time became deliberate, almost judicial; words were carefully selected. There was evident tension and restraint but no obvious show of emotion. A few moments later during a discussion of

rise in peripheral resistance and often marked by a fall in cardiac output.

CASE 2. For example, a 21-year old white female machine operator, one of identical twins had been known to have sustained hypertension over 8 years. This patient had weighed only 2½ lbs. at birth. Her identical twin's birth weight was 5½ lbs. Throughout early childhood, the patient had sustained frequent respiratory infections, including pneumonia and empyema. She had not only been in a disadvantageous position physically in comparison to her sister but she had also

been surpassed by her in school and later in employment status. The patient appeared to be tense, alert, overly eager to cooperate, quick moving, but very guarded in communication and markedly restrained in emotional expression. During the discussion of personal problems, especially in relation to her competitive relationship to her twin and to her heterosexual–social adjustment, blood

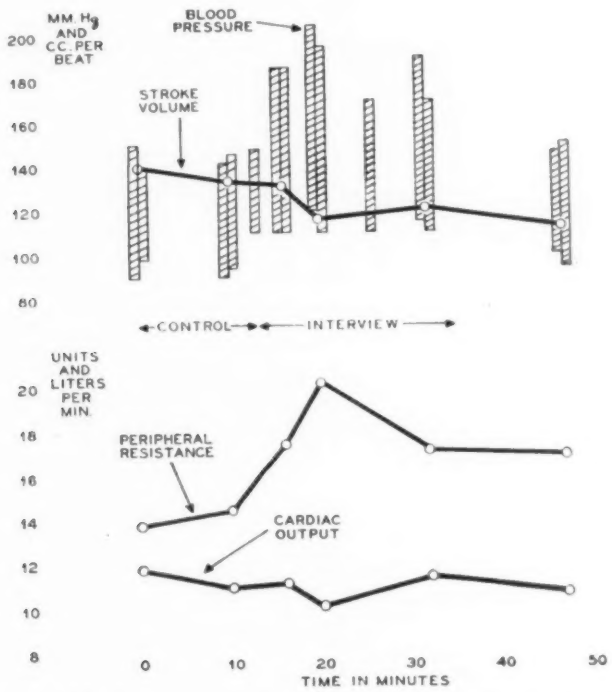

FIG. 4.—Elevation of blood pressure attributable to increased peripheral resistance during a period of suppressed anxiety and superficial composure in a hypertensive girl, one of identical twins. (Case 2)

pressure rose sharply accompanied by a corresponding increase in peripheral resistance and a fall in cardiac output, as illustrated in Figure 4. Following reassurance and diversion, the blood pressure fell to lower levels and peripheral resistance decreased.

SIMULTANEOUS MEASUREMENT OF RENAL AND GENERAL HEMODYNAMICS: In earlier communications were reported studies of renal hemodynamics during the stress of interviews similar to those described above[8,13]. Among both hypertensive and normotensive subjects an elevation of arterial pressure was observed consistently associated with a decline in renal blood flow and increase in filtration fraction. These changes were considered to reflect a vasoconstriction in the kidney, affecting chiefly the efferent glomerular arteriole. During the period of reassurance following the interview, the blood pressure usually fell to the control level, but the renal vasoconstrictor effect often persisted long afterward. Many of the hypertensive subjects thus tested also fell into the present series, and since the experiments were carried out in very similar fashion, it is likely that the hemodynamic effects were the

same in the two studies. The validity of that assumption was tested by performing, on two subjects, simultaneous measurements of general cardiovascular dynamics and renal blood flow both before and after partial thoracolumbar sympathectomy.*

CASE 3. A 45-year old Swedish housewife was referred to the clinic because of dizziness and headaches related to hypertension which had been first noted 16 years earlier during her first pregnancy. Episodes of dizziness were closely correlated with stressful incidents in her life such as disputes with her husband who was often drunk. At her first visit to the clinic, her blood pressure was 236/148. Her heart was moderately enlarged and there was a faint systolic murmur at the base. The electrocardiogram revealed a left axis deviation. The results of observations on this patient during an interview are shown in Figure 5. After a preliminary period of rest and relaxation in which there was no conversation the patient was engaged in a discussion of her marital life. She described her husband's alcoholism, its effect on her son, and her own feelings. She showed evident anxiety mingled with resentment and her blood pressure rose from 186/127 to 242/168. There was associated increase in heart rate, stroke volume and cardiac output. During this period, peripheral resistance fell from 89 to 43 units. Accompanying these changes there was a decrease in renal blood flow and an increase in filtration fraction. At the end of the interview the patient became quiet and apparently calm. Stroke volume and pulse fell but there was a persistent elevation of blood pressure associated with a sharp rise in peripheral resistance to 89 units. During this period renal blood flow remained decreased. Finally, blood pressure and peripheral resistance and renal blood flow all returned to essentially their original values.

COMMENT. It is noteworthy in this subject that the relatively free expres-

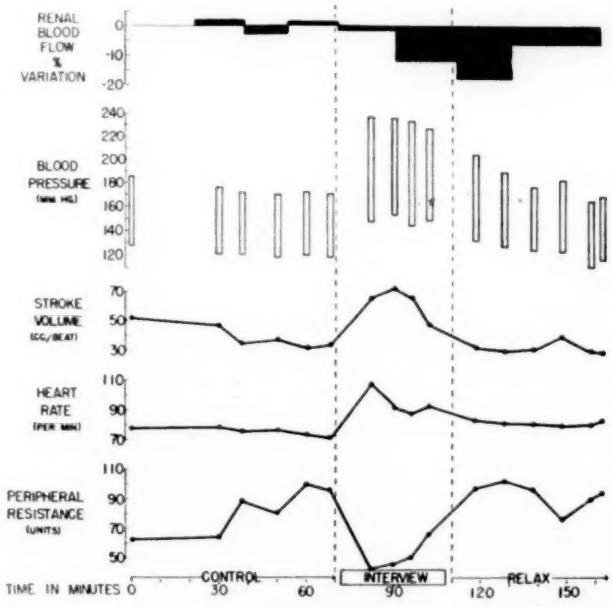

FIG. 5.—*Simultaneous measurement of renal blood flow and general hemodynamics in a hypertensive woman during a period of overt anxiety and resentment.* (Case 3) There occurred an increase in stroke volume, blood pressure and heart rate accompanied by a decrease in renal blood flow and in general peripheral resistance.

* We are indebted to Dr. John Pfeiffer for the estimations of renal blood flow by the techniques of Homer Smith[8].

sion of anxiety and feelings of hostility were associated with a blood pressure elevation which was accomplished chiefly by a rise in cardiac output, but that when the expression of the subject's feelings was blocked by concluding the interview, the blood pressure elevation continued and was attributable mainly to increased peripheral resistance.

Case 4. A 42-year old woman came to the clinic because of repeated episodes of dizziness. She was found to have hypertension in the neighborhood of 180/110. Physical and laboratory studies failed to reveal evidence of heart disease or other structural abnormality. Observations of systemic and renal circulatory dynamics in this patient during an interview were similar to those of Case 3. After an initial period of relaxation during which control observations were made, an interview dealing with her current conflicts was undertaken and her preoccupation with the behavior of her adolescent daughter was dwelt upon. The patient gained the impression that the interviewer was judging her and she became tense and resentful. Blood pressure rose from 160/110 to 220/136. The heart rate and stroke volume increased while peripheral resistance fell slightly from 36 to 30 units. Concomitantly there was a fall in renal blood flow of approximately 30% accompanied by an increase in the filtration fraction from 0.200 to 0.215, indicative of renal vasoconstriction. At the close of the discussion she was given friendly reassurance. The blood pressure and cardiac output returned toward their original values, but did not reach them before the close of the experimental period. Likewise, the renal blood flow remained reduced and filtration fraction elevated throughout the period of observation.

The Modification of Effects by Sympathectomy. The 2 patients just described were also studied after bilateral dorsolumbar sympathectomy. In the first patient the interview was accompanied by a rise in blood pressure as shown in Fig. 6. There was noted a preliminary increase in cardiac output without change in blood pressure. Later, when the blood pressure rose, peripheral resistance increased significantly. Following the interview, the patient was encouraged and became more relaxed. At this point the measured indicators fell again toward control levels until at the end of the experimental period when she became restless once more, the cardiac output rose again. There was no significant change in renal hemodynamics during this interview, a result duplicated by other observations on sympathectomized patients. In the second patient only general hemodynamics were measured. During a stressful interview she displayed a brisk elevation of arterial pressure from 150/100 to 180/120, tachycardia and an increase in stroke volume with a 50% fall in peripheral resistance. In other individuals the pressor response to stress after lumbodorsal sympathectomy was dependent chiefly upon an increase in peripheral resistance. For example, in one sympathectomized patient who displayed during the interview a rise in blood pressure of 142/88 to 184/138 there was a negligible increase in cardiac output but a marked increase in peripheral resistance which must be presumed to be attributable to humoral effects or to have occurred by reason of vasoconstriction in the areas of the body other than those whose sympathetic nerves had been interrupted.

Production of a Hypodynamic Response in Hypertensive Subjects. In previous studies[2,12] it has been pointed out that when stressful events are met with an attitude of resignation and despair, there is often a corresponding depression of cardiovascular function with reduction of cardiac output and variable changes in blood pressure and peripheral resistance. Similar results were occasionally found among the hypertensive subjects in whom such reactions of being overwhelmed were observed. In two of these instances blood pressure was elevated or sus-

tained despite a significant depression of cardiac output. In two other instances there was a lowering of blood pressure as well as a decrease in cardiac output. The following case is illustrative of this reaction:

Case 5. A 37-year old pregnant housewife was studied in the last weeks of an unwanted pregnancy. The patient was initially somewhat tense and anxious. Following preliminary measurements the patient was engaged in a discussion of her children and of the present pregnancy. She became disturbed by this and sobbed as she confessed to not wanting another child and resentfully blamed her husband for failure to cooperate in the planning of their family. Her blood pressure rose briskly but had fallen again before the patient became quiet enough to permit measurements of cardiac function. When these were made the stroke volume was found to be slightly elevated and the heart rate somewhat lower. Following further ventilation of her problems the patient became more relaxed and cheerful, but then she became restless and complained of back pain. The procedure seemed an unnecessary additional burden to her heavy load. When she was asked to put her hand in ice water for a cold pressor test she felt this to be "the last straw". She complied with the request but her blood pressure instead of rising, fell precipitously as did the heart rate and stroke volume to an even greater extent so that there was a slight increase in peripheral resistance, indicating some vasoconstriction.

Two weeks later the patient was again interviewed a week after the delivery of her

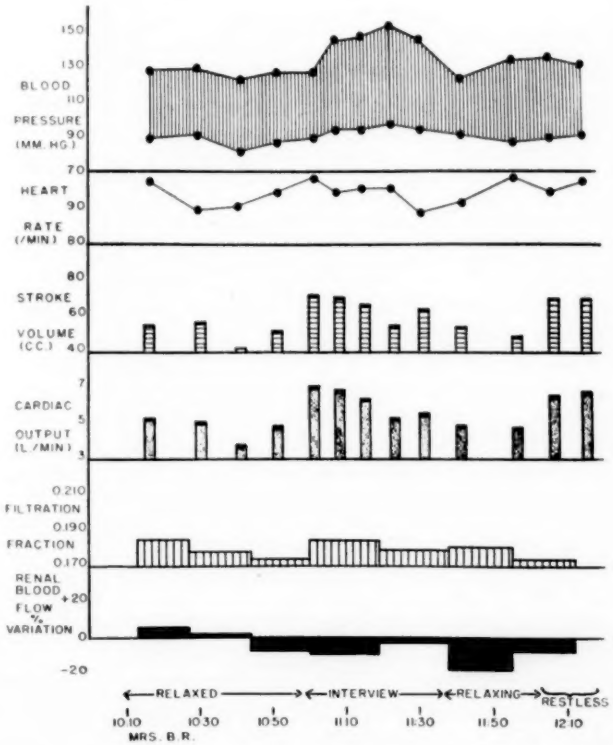

Fig. 6.—*Systemic and renal circulatory changes during anxiety after sympathectomy.* (Case 4) As anxiety developed during the interview the cardiac output rose before the blood pressure so that there was an initial fall in peripheral resistance (not shown in figure). Later the blood pressure rose without further increase in cardiac output. Following the interview the blood pressure and cardiac index fell until the patient became restless at the end of the procedure when they again rose. There was no significant change in renal hemodynamics.

baby. Her pride and pleasure in the baby had in the meantime completely altered her mood. At the beginning of the experimental period she was relaxed and cheerful. Her diastolic blood pressure had fallen from 115 to 96 and, associated with the delivery of her baby and decline in anxiety, her cardiac output was considerably less. When the subject of her pregnancy was touched upon, the patient became moderately anxious as she expressed a strong desire to avoid any further pregnancies. She was not, however, as disturbed as she had been previously by this topic. There was a smaller pressor response and slight increases in heart rate and stroke volume. When she was asked to take the cold pressor test she did so with some irritation but not with the same abject misery shown on the previous occasion. This time there was a brisk pressor response as well as an increase in stroke volume and cardiac output.

COMMENT. It has been shown by Cranston *et al.*[1] that the response during the cold pressor test is significantly greater following an interview in which stressful topics are reviewed than during control observations. The above observation and others reported elsewhere[13] accentuate the fact that the presence or absence of stress is not so important in determining cardiovascular responses as is the attitude of the subject toward the situation.

Thus it appears that the hypertensive subject is capable of a variety of cardiovascular adaptions to stress including changes in cardiac output and peripheral resistance in either direction.

In an earlier study it was possible to recognize in both normotensive and hypertensive subjects during significant anxiety a pattern of hemodynamic reaction described as hyperdynamic, and characterized by an increase in heart rate and stroke volume and accompanied by a lowering of peripheral resistance, but usually an elevation of arterial pressure, especially of the systolic reading[10]. It has been pointed out here that this pattern characterizes the hemodynamic adaptations to physical exertion. This "exercise pattern" was encountered among hypertensive subjects who had not exercised but who were displaying overt evidences of anxiety and tension. Despite the feature of elevated arterial pressure, this does not appear to be the pattern of cardiovascular response typical of essential hypertension. Essential hypertension rather is characterized by an increase in peripheral resistance and an elevation of diastolic pressure without much alteration in cardiac output either from rate or stroke volume. This latter pattern of cardiovascular adjustment was also observed under the stress of important personal conflicts but, instead of overt anxiety, it was usually accompanied by an attitude of restraint and an exterior of calm and composure.

Summary and Conclusions. 1. Exercise tolerance (during relaxation) was not significantly different in a group of 20 hypertensive and a group of 28 normotensive individuals. In both groups mean blood pressure was slightly elevated and peripheral resistance slightly lowered following the exercise.

2. During more or less overt emotional disturbances evoked by discussion of stressful life situations, both hypertensive and non-hypertensive individuals usually showed an increase in cardiac output, a rise in blood pressure and a fall in peripheral resistance. However, the hypertensive subjects showed a greater rise in blood pressure in proportion to the increase in cardiac output than did normotensive subjects, which suggests a greater vasoconstrictive response (or a lesser net vasodilator response) in this group. When the subject's reaction to a conflict situation was characterized by restraint and

overt anxiety was not a prominent feature, there was an even greater tendency to vasoconstriction with increase in peripheral resistance.

3. When, during stressful situations, the hypertensive subject considered himself utterly defeated or overwhelmed, a hypodynamic response was observed with fall in blood pressure, cardiac output or both.

4. Partial (thoracolumbar) or total sympathectomy apparently modified but did not abolish the various circulatory dynamic responses to stressful situations.

5. It appears that the hypertensive individual differs from the normal subject chiefly in displaying a greater tendency to vasoconstrictor reactions to stressful situations.

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THE VASODILATOR EFFECTS OF INTRAVENOUS PROCAINE IN PATIENTS WITH ISCHEMIC EXTREMITIES*

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The use of intravenous procaine hydrochloride as a peripheral vasodilator has long been suggested but has never, to our knowledge, been objectively evaluated in human experiments. Leriche[9] reported a clinical impression of warmth and "coloration" of the extremities following its intravenous use. Using the same mode of administration, Hazard[6] postulated a vasodilator action from the observation of decreased blood pressure. In the anesthetized dog, the same author[7] demonstrated plethysmographically that intra-arterial injection causes vasodilatation in an extremity. Using 5 to 10 mg. of procaine per kilo intravenously, Buetner[2] found a temporary drop in blood pressure of dogs which he ascribed to peripheral vasodilatation. Gordon[5], Dodd and Pfeffer[3] and Barbour and Tovell[1] have reported clinical experience with this drug, suggesting that it is useful in a wide variety of peripheral vascular diseases, including thromboangiitis obliterans and arteriosclerosis, both as a vasodilator and as an analgesic. In 4 of 27 patients treated for urticaria, in whom no vascular disease was present, State and Wangensteen[15] found evidence of vasodilatation in the increase in skin temperature of the lower extremities following intravenous therapy with procaine. However, there was no mention of either the degree of increase or the room temperature.

Since our object was to evaluate the use of intravenous procaine as a vasodilator in peripheral vascular disease, this study was confined to patients with ischemic extremities.

Methods. Eight men and one woman were studied. Their ages ranged from 24 to 61. Their diagnoses are given in Table 1. As will be seen in Table 1, 7 of the patients had previously had a reflex vasodilatation test[4] performed on the same digits used in the study. Five of the patients had had basal vascular tone tests[12]. Vasodilatation tests and vascular tone tests were performed on a day prior to the procaine administration. Each of the patients had at some previous time been treated with procaine and none had exhibited sensitivity.

The patients were studied by a previously outlined system[8,11,13,14] with observations made upon digital cutaneous blood flow, blood pressure, cardiac output, pulse rate and oral temperature. Each presented himself at least 4 hours after eating and was allowed a half-hour rest period prior to the test in a constant temperature room at an average temperature of 23.5°C. During this period physiological saline solution was administered intravenously at the rate of 60 to 90 drops per minute. When the skin temperature, blood pressure and pulse rate had become stable, 250 cc. of freshly prepared solution of 0.1 or 0.2% procaine hydrochloride in physiological saline solution were administered through the same apparatus at the same rate for a period of 10 to 70 minutes (see Table 1).

* This work was made possible by a grant from the U. S. Public Health Service.

TABLE 1.—CLINICAL DATA ON PATIENTS AND CARDIOVASCULAR CHANGES INDUCED BY INTRAVENOUS PROCAINE ADMINISTRATION

								Maximum Changes in:								
													Digital Cutaneous Blood Flow‡ cc/100 cc. digit/min.			
												Blood Pressure mm.Hg	Fingers		Toes	
Pt. No.	Subj.	Age	Sex	Diag.*	Basal Vascular Tone	Dosage of Procaine 0.1% Sol. Gm./Min's	Subjective Symptoms	Room Temp. °C	Oral Temp. °f	Pulse Rate	Cardiac Output °c	Syst.	Dias.	R	L	R	L
1	H. H.	47	M	ASO	High	0.5/70	0	22.9	0	−6	−7	0	+8	−3	−2	0	0
2	M. S.	61	M	"		0.075/10	Precordial pressure	23.6	0	−4	−15	0	+2	−16	−16	0	0
3	M. F.	47	M	"		0.5/45	0	23.0	0	0		+4	0	−1	−1	+2	−1
4	E. B.	53	F	R.P.	High	0.085/10	Nervous, restless, apprehensive, dry mouth, perioral numbness, twitching of eyelids.	23.5	−0.4	+4	−6	−4	0	0	−1	−1	+1
5	F. T.	44	M	TAO	High	0.55/55	0	24.0	−0.3	−4		−6	+10	−22	−20	0	0
6	G. B.	42	M	IVT	High	0.15/15	General body warmth, drowsy, light headed, floating away sensation.	23.4	0	+4	+16	0	0	+1	[illegible]	0	+0.5
7	C. M.	24	M	TAO		0.25/60	Mild pain relief.	23.6	+0.3	+4		0	+10	−18	−15	0	−1
8	B. B.	57	M	"		0.15/20	Drowsy, light headed.	23.7	0	0	+22	−16	−4	−18	−4	0	+7
9	W. B.	54	M	ASO	High	0.5/70	0	23.8	−0.2	−4	+30	−6	−8	0	0	+3.5	0
							AVERAGE	23.5	−0.1	−1	+6	−3	+2	−8.5	−8.4	+0.5**	+0.7**
							CONTROL†	21.6	−0.1	−3	−2	+1	+3	−7		−3	

* Diagnoses: 1. Arteriosclerotic occlusive vascular disease, absent left popliteal pulse.
2. Arteriosclerotic occlusive vascular disease, absent left dorsalis pedis, right popliteal.
3. Arteriosclerotic occlusive vascular disease, bilateral popliteal occlusion, ischemic ulcer right great toe.
4. Raynaud's phenomenon.
5. Thromboangiitis obliterans, absent left dorsalis pedis, posterior tibial.
6. Increased vasomotor tone.
7. Thromboangiitis obliterans, bilateral popliteal occlusion, perforating ulcer left great toe.
8. Thromboangiitis obliterans, absent right radial, ulnar, dorsalis pedis and posterior tibial.
9. Arteriosclerotic occlusive vascular disease, left popliteal occlusion.

** Only one significant increase in 18 determinations, in spite of fact that individual vasodilatation tests showed a definite capacity for significant increase of blood flow in all cases tested (see text).

† Six normals. Individual data published previously.[8]

‡ Fingers and toes were in a state of moderate vasoconstriction at the time the drug was administered as demonstrated by an average finger temperature of 26.7° and an average toe temperature of 24.5° C.

The subjects were observed for at least 30 minutes after the drug was discontinued. The skin temperature readings were converted by a previously established relationship[10] to cc. of blood flow/100 cc. of digit/minute. The data were compared to those of a control group[8] of 6 normals previously studied at an average room temperature of 21.6°C.

Results. Table 1 shows the collected data on the changes induced by intravenous procaine hydrochloride upon the blood flow in the fingers and toes, blood pressure, cardiac output, pulse rate and oral temperature.

The average change in blood flow through the fingers of the individuals in this study was a decrease of 7 cc./100 cc. digit/minute, corresponding closely to the change noted in the control group. In none of the 18 fingers studied was there a significant increase in flow. The mean change in the blood flow through the toes in the procaine-treated group was an increase of 0.6 cc./100 cc. digit/minute. This figure represents the average of 18 determinations in which there was only one significant increase in blood flow. Statistically this change is not significantly different from the average control decrease of blood flow of 3 cc/100 cc. digit/minute, in spite of the fact that there was a slightly greater stimulation for vasoconstriction in the control group, since the control measurements were made at a lower room temperature.

No significant changes were noted in the blood pressure, pulse rate or oral temperature.

Cardiac output as estimated from the ballistocardiograph showed changes in both directions in individual cases (see Table 1), but no definite trend in either direction.

Undesirable side effects were noted in 4 of the 9 patients treated with intravenous procaine hydrochloride. One patient complained of precordial pressure which disappeared within 3 minutes following the cessation of the procaine. Two noted a feeling of drowsiness and light headedness; one of these also complained of the sensation of "floating away." The fourth patient was extremely nervous, apprehensive, restless, complained of a dry mouth and perioral numbness, and showed marked twitching of the eyelids. In all 4 cases the symptoms subsided within 5 minutes of the discontinuance of the procaine infusion; in none of the 4 cases was there any change in the vital signs during the "procaine reaction."

A vasodilatation test was performed on 7 of the 9 patients in this study. In all 7 there was some increase in blood flow through the lower extremities during the test. In 5, a near "normal" capacity for blood flow and in 2, a clearly decreased capacity for blood flow were demonstrated. While the capacity to increase the blood flow was present in these individuals, the use of intravenous procaine hydrochloride did not produce a significantly increased blood flow through either the upper or lower extremities.

Discussion. The rates of administration and the amounts closely resembled those currently used clinically[1,3,5,15]. We believe we used full therapeutic doses. The side reactions kept us from further increasing the dose.

Summary. 1. Changes in digital cutaneous blood flow, blood pressure, cardiac output, pulse rate and oral temperature effected by clinical doses of intravenous procaine hydrochloride were evaluated in a group of 9 patients with peripheral arterial disease.

2. In 4 patients of the 9, undesirable side effects of the drug were noted.

3. Under the conditions of this study, procaine produced no significant change in digital cutaneous blood flow, blood pressure, cardiac output, pulse rate or oral temperature when compared with a normal group of controls.

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EVALUATION OF PAVERIL IN ANGINA PECTORIS*

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This study is a subjective and objective evaluation of the use of paveril phosphate, the synthetic analogue of papaverine, in the treatment of patients with angina pectoris.

Papaverine exerts a vasodilator effect[9] and has been used in recent years in the treatment of patients with coronary artery disease. Interest was stimulated by the work of Elek and Katz[2] in 1942 who reported definite improvement in patients with angina pectoris when adequate doses of the drug were given orally. Swanson[13] also reported favorable results. Gray, Riseman and Stearns[4], believed that oral papaverine was not useful in the treatment of angina pectoris. Katz *et al.*[12], in 1949 re-evaluated papaverine and found that the drug actually had limited value in this syndrome.

Paveril phosphate (6, 7-dimethoxy-1 - 4′ - ethyl - 3′ - methoxybenzyl - 3 - isoquinoline) is a non-narcotic substance. It has been shown to be equal to papaverine in its dilating effect on coronary arteries in dogs[6]. Toxicity studies in albino mice revealed that the drug is less toxic than papaverine when given intravenously or orally. No tolerance developed in either mice or dogs after administration[6].

Paveril phosphate was used by Best and Coe[1] in 11 patients with coronary artery insufficiency; they found symptomatic improvement in six patients with a return to normal of 35.4% of electrocardiographic tests. They felt that further experimental and clinical studies were warranted.

Method. Our present study was conducted on 13 former hospital patients in whom a diagnosis of angina pectoris had been established. All had a definite history of typical pain on exertion relieved by rest. Other criteria were a positive Master-Two-Step test or a history of old myocardial infarction with arteriosclerosis. The clinical records were reviewed and the patients were called to the hospital for examination on an outpatient basis. Only cooperative patients were selected.

All studies were done on males between the ages of 45 and 75 years whose symptoms were of 6 months to 2½ years duration. These patients were ambulant and the majority were working. They were permitted usual activities and usual medication, including nitroglycerin, during the period of this study.

Two materials were compared: enteric coated paveril phosphate, 200 mg., and an inert lactose placebo, indistinguishable in size, shape, and color from the medication to be tested. The medication was administered in doses of 1 tablet 4 times a day. There was an initial control period of 1 week following which placebo and paveril phosphate tablets were alternated weekly.

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For subjective evaluation the Daily Report Card, Method of Gold and associates[5] was used:

The patient indicated with a cross mark in the appropriate space on the card the degree of pain he had that day. These cards were returned to the examining physician at each weekly visit and a new card was issued. The patient was considered to be improved if his symptoms were 50% relieved.

Objective evaluation was attempted by 3 methods:

(1) The Flicker-Photometer, as described by Krasno and Ivy[7] who postulated that vasospasm of the retinal arterioles would be relieved by nitroglycerine and could be measured by an increase or decrease of visual acuity. An abnormal response resulted in an increase of visual acuity due to relief of vasospasm whereas, if vasospasm were not present, passive hyperemia of the retina occurred decreasing visual acuity.

(2) An Exercise Tolerance Test, according to the method of Riseman *et al.*[10], was done. In this procedure the patients rested 15 minutes and then walked up standard steps. The patient was instructed to stop the exercise at the beginning of anginal pain. The number of ascents which the patient made were recorded with pain as the end point. The patients were considered improved if the number of ascents increased by 50% over the control level.

(3) The single Master-Two-Step test[8] was also performed. Electrocardiograms were taken before exercise, immediately after exercise, 3 minutes, and then 8 minutes following exercise. These tracings were compared with the control. Criteria for a positive test were those of Master and his associates.

TABLE 1.—SUBJECTIVE EFFECT OF PAVERIL PHOSPHATE IN 13 PATIENTS WITH ANGINA PECTORIS

SYMPTOMATIC IMPROVEMENT

Patient	*Placebo*	*Pareril Phosphate*
H. H.	Yes	Yes
J. K.	Yes	Yes
F. H.	Yes	Yes
C. I.	Yes	Yes
E. B.	No	No
A. S.	Yes	Yes
J. V.	No	Yes
B. B.	Yes	Yes
H. P.	No	Yes
L. H.	No	No
F. F.	Yes	Yes
W. P.	No	No
G. M.	Yes	Yes

Results. The subjective effect based on analysis of the "daily report card" is shown in Table 1. Reduction of anginal attacks by 50% occurred in 8 patients while on placebo and on 10 patients while on paveril. Of these 10, 8 were also improved by placebo. No subjective improvement towards either placebo or paveril occurred in 3 patients.

Only 1 untoward reaction with paveril was observed. One patient with peptic ulcer had increased gastric symptoms.

Analysis of the results of the Flicker-Photometer test revealed that in the control study 12 patients had an abnormal Flicker response while 1 patient was normal. The test remained abnormal in 9 patients after placebo, became borderline in 2, and normal in 1. After paveril medication 7 patients reverted to normal, 3 became borderline, while 2 remained abnormal. These results are shown in Table 2.

The Exercise Tolerance test was performed in 11 patients. It was considered too dangerous to perform on 2 patients with severe angina. Improvement of 50% over the control period was observed in 5 patients on placebo, while 4 patients improved on paveril.

TABLE 2.—EFFECT OF PAVERIL PHOSPHATE ON FLICKER FUSION TIME

Patient	*Control*	*Placebo*	*Pareril Phosphate*
H. H.	A	A	N
J. K.	A	A	N
F. H.	A	A	A
C. I.	A	A	N
E. B.	A	B	N
A. S.	A	A	B
J. V.	A	A	N
B. B.	A	N	A
H. P.	A	A	N
L. H.	N	N	N
F. F.	A	B	B
W. P.	A	A	B
G. M.	A	A	N

A—Abnormal
B—Borderline
N—Normal

The 4 patients who exhibited improvement on paveril also improved with placebo. Six patients revealed no change towards placebo or paveril. These results are shown in Table 3.

The Master-Two-Step test was performed in 10 patients in the control period all of whom had positive results. After paveril medication 2 patients reverted to negative and 2 patients showed borderline electrocardiograms. In 1 patient we were unable to repeat the test. The results are contained in Table 3.

TABLE 3.—EFFECT OF PAVERIL PHOSPHATE ON EXERCISE TOLERANCE TEST AND MASTER 2 STEP TEST.

	Exercise Tolerance		*Master 2 Step Test*	
Patient	*Placebo*	*Paveril*	*Control*	*Paveril*
H. H.	U	U	+	+
J. K.	U	U	+	−
E. H.				
C. I.				
E. B.	I	U	+	+
A. S.	U	U	+	+
J. V.	I	I	+	+
B. B.	I	I		
H. P.	I	I	+	±
L. H.	U	U	+	
F. F.	U	U	+	−
W. P.	I	I	+	+
G. M.	U	U	+	±

U—Unchanged
I—Improved

Discussion. Evaluation of drugs for relief of anginal pain is a difficult clinical problem, particularly so because of the psychic effect of any sort of treatment. In this study almost as many patients noted diminution in symptoms with the placebo as with the drug under investigation. Only 2 patients received relief from paveril when the placebo was not effective. The objective tests used were made as free from subjective influences as possible.

An apparently favorable response to paveril was indicated by the Flicker Photometer. However, it is an improper assumption that the coronary arterioles respond in a manner similar to the retinal arterioles The value of this instrument in the diagnosis of coronary insufficiency has been criticized by Fox and Wright[3] and Russek *et al.*[11]. However, in our study 12 of 13 patients with known angina pectoris responded in an abnormal manner. The results of the Exercise Tolerance Test and Master-Two-Step test tended to confirm our impression that there was no significant advantage of the paveril over the placebo.

Since paveril definitely acts as a vasodilator in perfused coronary arteries in animals[6], its failure to produce clinical results in man may be on the basis of one or several mechanisms[12]:

a. Its action on the coronary arteries of man may be different from its action in animals.

b. Coronary dilatation may not be great enough, or neutralized by dilatation of other systemic vessels with which the coronary vessels form parallel circuits.

c. Factors other than inadequate coronary flow may be involved in the mechanism giving rise to anginal pain.

d. The dosage employed in our series was inadequate.

Summary. 1. The effect of paveril phosphate in reducing symptoms and signs of coronary insufficiency was studied in 13 patients with angina pectoris.

2. Subjectively, the patients did not receive significantly more benefit from paveril phosphate than from a placebo.

3. Objective tests revealed that paveril phosphate did cause retinal arteriolar dilatation as measured by the Flicker-Photometer, but negligible improvement was found on the basis of Exercise Tolerance and the Master-Two-Step test.

4. The oral use of paveril phosphate in the dosage employed has no value in the treatment of angina pectoris.

We wish to express our gratitude to Mr. George Prestash for his technical assistance.

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MANAGEMENT OF KHELLIN TOXICITY: EFFECTS OF DOSAGE AND PURIFICATION*

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In 1946, Anrep and coworkers[1] reported that khellin, a derivative of the plant, Ammi visnaga, was effective in the treatment of angina pectoris in man. They reported a low incidence of toxic side effects following the oral administration of pure khellin in an average daily dose of 120 mg. These investigators[2] warn that crude extracts of the plant cause undesirable side effects, particularly in the gastrointestinal tract. The effectiveness and low toxicity of pure khellin was subsequently confirmed by other investigators[5,6,10].

The plant Ammi visnaga contains 3 crystalline substances[3]. Khellin is the most important constituent since animal experiments show it to have a specific dilator action on the coronary arteries. Chemically it is $C_{14}H_{12}O_5$ with a melting point of 153° to 155° C. Visnagin differs from khellin in having a single methoxy group with a melting point of 142° to 145° C. and is less potent in relaxing smooth muscles. The final component, khellin-glucoside, is thought to be devoid of antispasmodic action and is not absorbed or converted to khellin. The melting point of this component is 175° C. It is thought that melting point determinations are a satisfactory guide to the purity of a particular khellin preparation.

Recent studies[4,7,14,15] have reported a very high incidence of toxic effects in the gastrointestinal tract of patients receiving a commercially available khellin preparation containing 70 to 80% khellin and 20 to 30% visnagin. These side effects have greatly limited the clinical usefulness of the drug.

It was thought advisable to study the effectiveness and side effects of a khellin preparation, containing a lessened amount of visnagin, in smaller doses than heretofore reported.

Method. Selection of Patients. Studies were made in a group of 10 patients with arteriosclerotic disease of the coronary arteries as evidenced by classical angina pectoris. This consisted of exertional substernal pain with typical radiation which was relieved promptly by rest or nitroglycerine.

The patients had been under constant observation for at least 1 year prior to this study. They had consistantly positive electrocardiographic tests for coronary insufficiency. The patients were selected from a larger group with coronary insufficiency on the basis of a complete intolerance to a crude khellin product administered during the past 6 months. This product is a mixture of 70 to 80% khellin and 20 to 30% visnagin, and was administered in a dosage of 120 mg. per day. The onset of severe symptoms of nausea, vomiting, or diarrhea had precluded its further use despite the fact that clinical improvement in the anginal symptoms had occurred.

Medication. A crystalline khellin preparation, largely devoid of visnagin, was used in this study. Identical tablets were prepared containing 10, 20, 30, and 40 mg. of crystalline khellin and administered 3 times a day, after meals.

The analysis of the khellin product is as follows:

All patients initially received placebo tablets indistinguishable from the medication, and these placebo tablets were administered between all drug periods. The patients were studied following 18-day periods during

* Aided by a Grant from Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

Total Khelloids (Ultraviolet)	20 mg. tablets: 101.0%	10, 30, & 40 mg. tablets: 99.9%
Melting Point	149° to 154°	147.5° to 151.5°
Khellin/Visnagin Ratio	98.3/1.7	98.7/1.3
Toxicity (LD–50) (200 gm. Rat)	125 mg./Kg.	125 mg./Kg.

which time they received placebos, 30, 60, 90, or 120 mg. of crystalline khellin per day. An additional period consisted of the administration of 120 mg. per day for 18 days immediately followed by 30 mg. per day for 18 days, in an attempt to determine the utility of a "maintenance plan" of khellin therapy.

The order of administration of the tablets was varied from patient to patient and was unknown to the patient and the examiner conducting the electrocardiographic tests. All patients remained ambulatory and undertook their usual activities throughout the period of study.

Electrocardiographic Evaluations. All electrocardiograms consisted of Leads I, II, III, and V_4, simultaneously recorded by means of a four-channel Sanborn Poly-Viso Electrocardiograph.

1. Exercise Tolerance Test. All patients rested 15 minutes and a control electrocardiogram was recorded. The patients were then exercised on the Standard Steps of Master[13] until they experienced typical anginal pain. An immediate electrocardiogram was recorded. If this were positive, the number of trips necessary to produce the changes was recorded. If it were negative, the test was repeated at the same dosage level on another day. In all patients, pain *and* a positive electrocardiogram constituted the end point for the evaluation.

Criteria for a positive test consisted of a depression of the RS-T junction of at least 1 mm. in any lead, or conversion of an upright T wave to an iso-electric or inverted T in Leads I, II, or V_4.

2. Anoxemia Test. A control electrocardiogram was recorded. A reduced oxygen mixture, consisting of 10% oxygen and 90% nitrogen, was administered by means of a McKesson gas machine which was equipped with a flutter valve so that no rebreathing of the mixture occurred.

The reduced oxygen mixture inhalation was administered until pain *and* a positive electrocardiographic response occurred. This time, in minutes, was then recorded. In a few instances following treatment, the patient experienced no pain and the electrocardiogram remained unchanged after 20 minutes of anoxemia; this was then recorded as a normal test. This plan was necessary because of the reluctance on the part of the patients to submit themselves to more prolonged inhalation of the reduced oxygen mixture.

Criteria for a positive test were similar to those described by Levy[12]. The sum of the RS-T depressions in all leads exceeds 3 mm. or the direction of the T waves in Leads I or V_4 is reversed and accompanied by a depression of 1 mm. or more of the RS-T complex.

Toxic Symptoms. The appearance of nausea, vomiting, anorexia, vertigo, or insomnia, was considered to be a toxic symptom if it occurred while the patient was receiving crystalline khellin and disappeared soon after the substitution of placebo tablets. The symptoms were arbitrarily graded from 1 to 4 plus on the basis of severity and the degree to which they incapacitated the patient.

Results. A. Electrocardiographic Tests. The effects of crystalline khellin on the exercise tolerance of the 9 patients tested are summarized in Table 1. The administration of khellin in the various dosages was accompanied by an increased ability to delay pain and abnormal electrocardiographic responses in 40 of 42 (95.2%) instances. There is no apparent direct relationship between dosage and exercise tolerance. One patient, M. B., was not tested because of severe rheumatoid arthritis. Patient H. S. died during the study, and patient F. H. was unable to tolerate the larger doses of khellin.

The effects of crystalline khellin on the anoxemia test are summarized in Table 2. The ability to delay pain and an abnormal electrocardiographic response was noted in 41 of 47 instances when compared to the placebo period. Normalization of the test occurred in

Effects of Khellin on Exercise Tolerance

Patient	NUMBER OF TRIPS ON STANDARD MASTER'S STEPS						
	Control	Placebo	Khellin – mg. per day				
			30	60	90	120	120 - 18 days 30 - 18 days
A.G.	16	13	29	20	18	29	26
F.W.	16	14	30	18	20	30	23
J.J.	20	24	26	30	26	36	26
T.H.	14	16	26	19	18	18	18
H.S.	18	21	–	30	31	33	30
M.D.	8	8	19	18	22	20	18
J.H.	15	15	19	19	19	15	15
M.L.	18	21	26	24	28	28	26
F.H.	6	6	16	18	16	–	–

Table 1.—The effects of khellin in varying dosages in exercise tolerance. The number of trips necessary to produce pain and a positive electrocardiogram is recorded in each instance.

Effects of Khellin on Anoxemia Test

Patient	MINUTES OF ANOXEMIA						
	Control	Placebo	Khellin - mg. per day				
			30	60	90	120	120 - 18 days 30 - 18 days
A.G.	4	6	10	5	7	18	12
F.W.	10	14	N	N	14	N	16
J.J.	18	16	N	N	N	N	20
T.H.	10	6	8	8	19	18	16
H.S.	6	9	–	20	20	12	9.5
M.D.	3	4	5	5	12	7	10
J.H.	8	10	N	N	N	9	10
M.L.	19	18	20	14	N	N	20
F.H.	4	4	6.5	8	10	–	–
M.B.	4	5	8	4	6.5	7	6

Table 2.—The effects of khellin in varying dosages on the ability to undergo anoxemia. The number of minutes necessary to produce pain and a positive electrocardiogram is recorded. N refers to those patients who completed 20 minutes of anoxemia without abnormal changes in the electrocardiogram.

12 of 47 (25.5%) instances. Again there appears to be no significant advantage following the larger doses of khellin.

B. Toxic Effects. Table 3 summarizes the incidence of undesirable side effects of khellin administration. In general, there appears to be a close relationship between the incidence and severity of toxic effects and the larger doses of khellin.

Discussion. Side effects incident to the use of commercially available khellin are of such frequent occurrence and severity as to greatly reduce its usefulness in the management of angina pectoris. Initially, our attention was directed to the possibility that a local irritant action on the gastric mucosa was the major factor. However, studies in which khellin was administered in an enteric coated form[7] and in combination with phenobarbital or aluminum hydroxide[8] revealed no lessened incidence of these side effects. It is likely that toxic manifestations are an essential feature of overdosage with any active khellin preparation. In some patients the toxic and therapeutic doses are almost identical so that any empirical dosage is not advisable with any khellin preparation.

Tolerated doses of khellin cannot be predetermined on the basis of body weight. Patients A. G. and M. L. both weighed over 180 pounds yet were intolerant of the 120 mg. daily doses of khellin, whereas this same dose was well tolerated by patients J. J. and H. S., each of whom weighed less than 120 pounds. It appears that individual

TOXIC EFFECTS FOLLOWING KHELLIN ADMINISTRATION

Patient	Khellin – mg. per day				
	30	60	90	120	120 – 18 days 30 – 18 days
A.G.	+	+	+++	+++	+
F.W.	0	0	0	+	0
J.J.	0	0	+	0	0
T.H.	0	0	+	+	0
H.S.		0	0	0	0
M.D.	+	+++	++	+++	++
J.H.	0	0	+++	+++	+
M.L.	0	+	+++	++++	0
F.H.	++	+++	+++	++++	++++
M.B.	0	0	++	++	+

Table 3.—The toxic effects of the crystalline khellin from which most of the visnagin had been removed. The most troublesome side effects were nausea and vomiting.

patients differ greatly in their tolerance to khellin.

The khellin used in this study was a purified crystalline khellin from which a large portion of the visnagin had been removed. Visnagin is not as effective a vasodilator as pure khellin[3] and may contribute to the toxic side effects. It will be noted that 2 patients who were completely intolerant to the administration of 120 mg. per day of a crude preparation were able to tolerate a similar dosage of the purified khellin. However, 8 patients noted little or no improvement in side effects with the crystalline preparation. This may indicate that purification of the khellin preparation is desirable, but will probably not solve the problem of toxicity in the majority of patients.

The data suggest that khellin may be effective in smaller dosage than usually recommended. This is of particular interest since toxicity seems to be less with the smaller dosage. It will be noted that the toxic effects seem to vary directly with the amount of khellin administered, whereas clinical effectiveness, as determined by this method of testing appears essentially the same with all dosage levels.

It would be desirable to have studied blood levels of khellin in these patients. It is possible that the results herein reported may represent a cumulative effect of khellin, in that its excretion may not have been complete during the 18 day placebo period. However, the commonly used alkaline hydrolysis[3] method gives unreliable results[11] and the biological method[3] can not be adapted readily to a quantitative procedure. Recently a polarographic method[9] has been reported which may be satisfactory for clinical use.

The method of evaluation, using pain and an abnormal electrocardiographic response to exercise and anoxemia, is not unobjectionable. It is evident that patients with severe side effects of nausea and vomiting are not in a basal state for testing and, to some extent, the stress agents are artificial; this is particularly true of the anoxemia test. In spite of these disadvantages, we know of no other objective method to discern differences in the effects of the various dose levels.

Symptomatic improvement is very difficult to evaluate in angina pectoris. In the past, we have used a daily tabulation of nitroglycerine requirements as an index of improvement. This is no longer useful since we encourage the patients to use nitroglycerine prophylactically. It may be of interest to note that 6 of the patients requested continuation of the drug in a dosage of 30 mg. per day at the completion of the project, and they considered the drug to be beneficial.

One patient, H. S., died apparently of acute myocardial infarction while receiving khellin in a dosage of 30 mg. per day. It is possible that the increased activity following the relief of pain by the drug may have resulted in his death. It seems more likely, however, that this episode merely represented the termination of the natural course of the disease. We have no evidence to suggest that the death resulted from a direct action of the khellin.

The value of khellin in the routine treatment of angina pectoris remains unestablished. The data herein reported represents a select group of patients in that they had been clinically benefited by previous administrations of a crude khellin, but its use had been limited by toxicity. We are of the opinion that khellin will find a place in the treatment of a small percentage of patients with the anginal syndrome. It is entirely possible that the utility of khel-

lin may depend on the adequacy of the collateral circulation available to the myocardium.

Summary. 1. Khellin may be effective in doses as low as 30 mg. per day. A similar ability to delay pain and abnormal electrocardiographic response to exercise and anoxemia was noted with khellin doses ranging from 30 to 120 mg. per day.

2. Toxic side effects of khellin depend to a great extent upon the daily dosages.

3. Elimination of the visnagin was accompanied by a lessened incidence of side effects in 2 of a series of 10 patients.

4. It would seem that purification of khellin is desirable, but attention should be paid to the establishment of a minimum effective daily dose for each patient.

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THE RELATIONSHIP OF CHRONIC PEPTIC ULCER TO CORONARY THROMBOSIS*

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AND

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Although peptic ulcer and coronary thrombosis with myocardial infarction are among the most common major illnesses encountered by the internist, clinical investigations of the relationship between these 2 diseases reported in the English-speaking medical literature, searched for the past 25 years, are rare. In the European literature Junet[10], Hochrein and Schleicher[7], and Laubry[11], have mentioned an increased incidence of coronary artery disease in chronic peptic ulcer. On the other hand, other observers such as Shaffer[22] failed to note this increase.

The late Banting and co-workers[6,12] demonstrated that prolonged stimulation of the vagus nerves in dogs produced coronary thrombosis with peptic ulcers in most instances. Hall *et al.*[6] and Manning *et al.*[12] also showed that the daily administration of acetylcholine or eserine would also consistently produce this combined disease of the coronary arteries and ulcers of the stomach and small intestine.

Since Morrison and Swalm[14,15] and others[27,9] had demonstrated the physiologic effects of the viscerocardiac reflex[28,20,4] in human subjects, we were further interested in studying the end results or pathologic changes occurring in combined lesions of the stomach and coronary arteries. Accordingly, the authors undertook such a study which included an analysis of the postmortem records of the Los Angeles County General Hospital for the past 15 years.

Influence of Diet on Coronary Disease. A corollary inquiry was made into the reports of observers[21,5,3] that an inordinate amount of milk and cream feedings required in most ulcer diets was conducive to the development of angina pectoris and coronary thrombosis as manifestations of coronary arteriosclerosis. This was based on the concept that dietary factors are important in the pathogenesis of arteriosclerosis. Snapper[23] has pointed out the rarity of atherosclerosis in the Chinese whose diets are very low in fat content; Steiner has recently pointed this out in Okinawans[24] and Hueper[8] has also reviewed this dietary evidence exhaustively. Moreton[13] has demonstrated that the serum colloid changes in the alimentary hyperlipemia which follows a fatty meal are directly contributory to the development of human atherosclerosis. As Snapper[23] and

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Heuper[8] have indicated, those nationalities who have been on very low fat diets tend to have a lowered serum cholesterol and lipid content. Steiner[25,26] and Adlersberg, Paretz and Boas[1], Morrison, Hall and Chaney[16], and others have shown that hypercholesterolemia predisposes to the development of atherosclerosis. Dock[5] and Plotz[21] have described the resultant exacerbation of angina pectoris, with or without a coronary thrombosis, in susceptible individuals who were placed on a Sippy regime with frequent milk and cream feedings, because of peptic ulcer. On the basis of such cases, the advisability of the Sippy diet has been questioned in middle-aged or older patients. Because of the above considerations, not only did we study the pathologic relationship of peptic ulcer and thrombosis, but we conducted a survey of blood lipid chemistry with chylomicron and lipomicron counts on a series of 20 patients with peptic ulcer before and after they were placed on a Sippy diet with feedings of 6 ounces of both milk and cream (half and half) every 1 to 2 hours in between meals for periods ranging from 1 to 3 months. The details of this investigation are the subject of a separate communication, but it may be said here that in general, considerable increases in chylomicron and lipomicron counts, serum neutral fats and total lipids occurred during the periods of milk and cream feedings. On the other hand, the fasting serum levels of cholesterol and phospholipids did not undergo significant increases in the periods studied, that is, from 1 to 3 months. Whether this latter is still true over longer periods of time has yet to be determined. It appears that the hypercholesterolemia produced by feeding in the experimental animal as shown by Steiner[25], Broun, *et al.*[2], Morrison and Rossi[17,18] and others cannot be duplicated in short term studies by the Sippy diet in human subjects, although the chylomicrons and lipomicrons and total serum lipids do rise to a high degree.

A search was made into the records of chronic peptic ulcer patients to determine whether they were more prone to the development of coronary thrombosis with myocardial infarction than a control series of patients who died of an acute illness and a control series of patients who died of a chronic illness.

Results. Tables 1A-C show a breakdown of the 339 cases studied according to the decade in which death occurred, the number of cases which showed a past coronary thrombosis from age 20 to 75, and myocardial infarction in each decade as well as the division of sexes and the incidence of myocardial infarction for the sexes.

One hundred sixteen consecutive cases of both sexes were then studied in which death was due to some complication of chronic peptic ulcer such as perforation, pyloric obstruction or hemorrhage. In Table 1A describing this group, it is noted that 24% of the 86 males with a mean age of 57 had a past coronary thrombosis with myocardial infarction at autopsy whereas 20% of the 30 females with a mean age of 59 were reported by the examining pathologist to have had previous myocardial infarctions.

Table 1B presents a control series of 71 consecutive cases of both sexes in whom death had occurred of an acute illness other than coronary thrombosis or peptic ulcer, suicide, accident or trauma. The acute illnesses included acute perforated appendicitis with peritonitis, intestinal volvulus, acute hemorrhagic pancreatitis, acute peritonitis, ileus, septicemia, etc. As shown in this table, 12% of the 43 males with a mean age of 50 and 4% of the females

with a mean age of 52 had a past coronary thrombosis with myocardial infarction at autopsy.

Table 1C presents an additional series of controls consisting of 152 consecutively studied cases who died of a chronic illness other than peptic ulcer or coronary thrombosis. Death had occurred from a chronic disease such as systemic and pulmonary tuberculosis, bronchiectasis, chronic cholecystitis with empyema, osteomyelitis, summarized data in Table 1 indicated that the incidence of myocardial infarctions among patients with chronic peptic ulcer was significantly greater than among those with other diseases (both acute and chronic). The p values were far less than 0.001 in all the comparisons. Inspection of the data distributed as to sex and age decades showed that the incidence of myocardial infarction varied in much the same pattern for all the groups.

TABLE 1.—INCIDENCE OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

A. In Chronic Peptic Ulcer

Ages by Decade		*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–75*				
	No. of Cases	*Myoc. Inf.*						*Total*	*Myoc. Inf.*	*%*	*Mean Age*
Sex M	1	0	10 1	15 0	16 4	23 9	21 7	86	21	(24%)	57
Sex F	1	0	1 0	5 1	6 1	10 2	7 2	30	6	(20%)	59
								116	27	(23%)	58

B. In Acute Diseases

		20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–75*				
	No. of Cases	*Myoc. Inf.*						*Total*	*Myoc. Inf.*	*%*	*Mean Age*
Sex M	8	0	6 1	4 0	9 1	8 2	6 1	43	5	(12%)	50
Sex F	2	0	5 0	6 1	5 0	5 0	5 0	28	1	(4%)	52
								71	6	(8%)	51

C. In Chronic Diseases

		20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–75*				
	No. of Cases	*Myoc. Inf.*						*Total*	*Myoc. Inf.*	*%*	*Mean Age*
Sex M	12	0	13 1	21 1	21 3	9 1	13 4	89	10	(11%)	50
Sex F	5	0	16 0	8 0	11 1	14 5	9 1	63	7	(11%)	51
								152	17	(11%)	50

ulcerative colitis pyelonephrosis, cirrhosis of the liver, *et cetera*. In this group 11% of the 89 males with a mean age of 50 and 11% of the 63 females with a mean age of 51 had a past coronary thrombosis with myocardial infarction.

A simple comparison of the percent incidence of myocardial infarction is shown in Table 1 for the chronic peptic ulcer series and the controls; the comparison was made since each group was similar in distribution of age decades and sexes in which death occurred.

Statistical Significance. Statistical analysis by the chi-square test of the

Discussion. Evidence for the increased incidence of coronary thrombosis with myocardial infarction in chronic peptic ulcer would seem to have first been suggested in the experimental studies of Hall, Manning, and Banting[6,12]. From their studies it would appear that reflex stimulation along the vagus nerves may induce peptic ulcer and/or coronary thrombosis with myocardial infarction in the human subject as well as in the experimental animal.

Etiologic Possibilities, Psychosomatic and Dietary. Several other possibilities also exist in this considered

relationship between peptic ulcer and coronary thrombosis. A psychosomatic factor may occur if coronary disease with angina or infarction comes first since the anxiety involved may lead to the association of peptic ulcer. It is also possible that both peptic ulcer and coronary thrombosis may be related, not to each other, but to a common background of hypothalamic disturbance. Finally, it is possible that a rise in total serum cholesterol and lipids on prolonged Sippy diets may contribute to the coronary thrombosis and myocardial infarction. If this latter point can be proven, then serious consideration should be given to the administration of milk substitutes in the Sippy regime, such as protein supplements, antacid gels, and the like.

ROLE OF THE VAGUS NERVE. Previous studies by the senior author demonstrated the effects of gastro-vagal stimulation in producing coronary artery spasm in human subjects. It was then and is now suggested that chronic peptic ulcer may mediate physiopathologic changes in the coronary arteries through the vagus nerves. The beneficial effects of atropine and its derivatives were then also reported in gastrointestinal patients subject to disorders of the coronary arteries such as angina pectoris.

The new parasympatholytic and anticholinergic drugs to depress vagal activity introduce the possibility that they may be therapeutically useful in these conditions. If this should prove to be the case, it is important that these drugs be administered in adequate dosage to ensure therapeutic effectiveness.

Summary. 1. The incidence of coronary thrombosis with myocardial infarction was found to be significantly increased in patients who died from chronic peptic ulcer.

2. The possible causes for this increased incidence are discussed.

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ON THE RELATION BETWEEN THE SITE OF VALVULAR INVOLVEMENT IN ENDOCARDITIS AND THE BLOOD PRESSURE RESTING ON THE VALVE

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It is a well known fact that valvular deformities as a sequel of rheumatic or bacterial endocarditis are much more common in the left than in the right half of the heart. Various explanations have been offered for this distribution; differences in the oxygen concentration of the blood, in the vascularization of the valves and in the pressure which these valves must bear when closed have been suggested as an explanation. Of these factors, the latter seems most probable[8]. If this factor is effective in all cases, there should be a direct relationship between the incidence of valvular involvement and the pressure resting on each valve when it is closed. Now that the technique of cardiac catheterization has enabled the exact determination of systolic and diastolic pressures not only in the greater, but also in the lesser circulation, such a comparison appeared justified.

A calculation was made of the incidence of involvement of each valve as a percentage of a total of 1024 published autopsy cases of valvular disease caused by endocarditis[2,4,7,9]. The mitral valves were involved in 86%, the aortic valves in 55%, the tricuspid valves in 19.6%, and the pulmonary valves in 1.1% of the cases. The average blood pressure which normally rests on the mitral valve when this is closed is the left ventricular systolic pressure, which is equal approximately to the systolic systemic arterial blood pressure; this was found to average 116 mm. Hg in about 90,000 normals[1,8]. The pressure resting on the aortic valves is the diastolic arterial systemic pressure, which was found to have an average value of 72 mm. Hg in the same material. The pressure resting on the tricuspid valve is the systolic right ventricular pressure, which was found to average 24 mm. Hg in 70 normals[3,5,6]. The pressure resting on the pulmonary valves is equal to the diastolic pulmonary pressure (found to average 7 mm. of Hg in the same material), minus the diastolic ventricular pressure (2 mm.); the net pressure thus equals 5 mm. Hg. If these pressures are correlated with the incidence of involvement of the corresponding valve, a factor of 1.3 is obtained for the mitral, aortic and tricuspid valves alike. Only in the case of the pulmonary valve the factor is 4.5, indicating that the incidence of involvement of this valve is less than would correspond to the pressure acting on this valve. This discrepancy could be explained by assuming that there is a minimum pressure which is necessary for the appearance of endocarditis, and that this pressure is not reached in the case of the pulmonary valve in the great majority of the cases.

There are several mechanisms which may be responsible for the relation between the pressure resting on a valve and the appearance of endocarditis in this valve. This pressure determines the force with which the edges of the valve are held together when this valve

is closed, and therefore the force with which the bacteria circulating in the blood stream are forced into the endothelial lining at these edges. The resistance of these cells against the bacteria may be influenced unfavorably by the mechanical force acting on the cells. Finally, the mechanical stress to which the connective tissue of the valves is subjected may accelerate and intensify its allergic reaction or the formation of scar tissue. It is well known that muscular and articular rheumatism normally appears first in those muscles, tendons and joints which are subjected to the greatest use. On the other hand, it is established beyond doubt that connective tissue is influenced in its formation by the intensity and direction of mechanical stress which is present in the tissue.

Summary. The pressure acting on a cardiac valve appears to be the chief factor in determining the involvement of this valve in rheumatic or bacterial endocarditis, as there is a direct relationship between these two variables.

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THE BENEFIT OF RESPIRATORY EXERCISES IN THE EMPHYSEMATOUS PATIENT*

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Dr. R. C. Newton, a Vice President of the American Climatological Association in 1899, in a paper before the Sixth Congress of American Physicians and Surgeons in 1903 said that "the medical profession has too meagre knowledge on the subject of deep breathing as a valuable therapeutic measure in a great variety of conditions."

There is no great problem in recognizing emphysema. A physician from a large chest service in this country stated "we can diagnose emphysema but we don't treat it."

It is beyond the scope of this brief paper to outline the theories regarding the mechanisms that produce emphysema. The major features of this condition center around the loss of alveolar elasticity. The respiratory and circulatory readjustments are an attempt to compensate for this loss. Christie[2] has shown that in emphysema the intrapleural pressure is not always negative throughout the respiratory cycle as it is in health, but approaches that of the atmosphere. Because of the inability of the lungs to retract during expiration, there is an increased amount of air in the lungs which keeps them in a permanent state of distension close to the confines of the thoracic cage, even infringing on the abdominal cavity by downward pressure on the diaphragm. The residual air which accumulates in the vesicles is at the expense of the vital capacity, and the vital capacity may closely approximate the resting tidal air, so that an individual at rest may be comfortable, but during any exertion he may have severe respiratory distress.

In essence, the functional impairment in emphysema may be stated as follows: "The muscles of inspiration are already in the inspiratory position when inspiration commences. A greater amount of work is required to distend the lung, and a large proportion of the air which is inspired is wasted on the functionless peripheral alveoli. Even after this wasted effort, the lungs cannot passively relax except as the result of an unnatural expiratory effort. As respiratory compensation fails, imperfect aeration of the blood occurs, and a vicious circle is established, with increasing demand for hyperventilation and decreasing ability to ventilate." (Christie)[3]

In summarizing the mechanics and physiology of emphysema, it is apparent that the lung volume is greatly increased, the residual air greatly increased, the ventilatory exchange greatly reduced, and the vital capacity is usually reduced. The maximum breathing capacity is always considerably below the estimated normal.

As the early stages of emphysema are not recognizable, it is almost impossible to prevent or to retard its gradual and sometimes rapid develop-

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ment, and in the treatment of the established state most measures have been without effect.

While working in the Charles Austrian Chest Clinic at the Johns Hopkins Hospital we saw many such patients and for a time we felt completely frustrated. Many of these individuals had associated bronchitis and bronchiectasis. In endeavoring to cope with these cases, we assumed, and probably falsely, that if something could be done to reduce the residual air and also the lung volume, that these patients might be helped. We were aware of the use of snug abdominal binders and the benefit sometimes derived from them, even though such benefit was usually transitory. The abdominal binder is at best a rather static agent. The work of the Asthma Research Council in England[1] was well known, outlining the exercises introduced by Tudor Edwards and his physical therapists at the Brompton Hospital. It seemed possible that some such exercises might be employed, stressing upper abdominal and lower thoracic breathing thus bringing the diaphragm into a more active role during respiration. Miss Miriam Miller, who had just come to our Physical Therapy Department at that time, was an enthusiastic aide in the teaching we planned. We explained what we wanted and she devised the series of exercises that we now employ.

Material. In the past three and a half years we have taught these special respiratory exercises to more than 235 patients who have emphysema. Most of these patients have had an associated bronchitis. We are not considering cases with associated bronchiectasis. Our patients are for the most part from the older age groups, 50 to 70 years of age, though a goodly proportion are in the 40 to 50 year age group. They have come from all walks of life, rich and poor alike. Those who have led a sedentary existence and those who are doing manual labor have been instructed in these exercises. The degree of intelligence is not an important factor, because we have had considerable success even with patients with less than average intelligence.

Method. It is of paramount importance to impress upon the patient that his breathing mechanism can be helped. It is then demonstrated to the patient that instead of struggling to make the thorax move, it is much simpler to use the abdominal muscles. Then it is demonstrated to him that the expiratory phase of respiration is the important feature, and instead of being passive he is able to make it active, with the result that the inspiratory phase becomes passive rather than active. It has been a surprise to us to observe how rapidly these patients can accommodate their respirations to conform with this newer concept. In fact, this type of respiration is carried over into sleep and has been seen to be maintained under anesthesia.

The first signs of improvement are the feeling of well being, the confidence that they are able to breath, the subsidence of respiratory effort and the lessening of dyspnea. In fact the improvement is subjective, rather than objective. In selected cases studied with spirometry, we have demonstrated no consistent and conclusive results. Studies of vital capacity have been done routinely but have not shown an increase commensurate with subjective improvement. One fairly consistent result has been some improvement in the maximum breathing capacity.

The following explanation of the exercises is given to each patient. This treatment is useful in chronic chest diseases in which there has developed constant outflow obstruction. This applies also to asthma of long duration which has resulted in obstructive emphysema more severe than the paroxysmal episodes of asthma. The purpose of the treatment is to re-educate the respiratory pattern to an involuntary continuous function in which emphasis is placed on expiration as the active phase and inspiration as the passive phase. It is emphasized that there is no set of exercises which can be mimeographed and handed to patients to be done at home. The importance of individual differences and the day to day developments cannot be overemphasized nor can they be anticipated. Therefore, each patient is a different problem and the specific prescriptions are made every day according to progress made and stumbling blocks which develop.

Instruction is given to the individual patient, progressing through the following list of exercises:

1. Patient in supine position with minimal elevation for comfort.
   (A) Teach easy corrected breathing: air expired through mouth, air inspired through nose; chest relaxed; throat relaxed; abdominal contracting to produce expiration actively; abdominal relaxing to allow inspiration passively.
   (B) Deepen both phases by increasing expiration.
   (C) Add retraction of lower ribs to abdominals in expiration.
   (D) Teach these with the patient lying on his side, right and left.
2. Patient in sitting position, knees apart for stability, arms relaxed.
   (A) Correct posture and teach exercise 1 (A).
   (B) Add exercise 1 (B), maintaining all corrections.
   (C) Add exercise 1 (C), usually an easy step.
3. Patient in standing position against wall.
   (A) Correct posture without adding tension.
   (B) Teach exercises 1 (A), 2 (A), 1 (B), 2 (B).
   1 (C) and 2 (C), progressing only as skill and accuracy are maintained.
4. Teach walking coordinated with easy respiration.
5. Teach lifting and replacing small objects of light weight.
6. Eliminate mouth breathing in expiration except in deep exercise.
7. Teach stair climbing: 2 to 4 steps with expiration, 1 or 2 with inspiration.
8. Translate all usual every-day activities into breathing pattern.
9. An optional procedure is to teach mild posture exercises in all positions within breathing pattern.
10. Encourage gradual increase in walking and stair climbing as criteria of improvement.

No progression of activity must be made until each previous skill is mastered. Practice sessions between treatments are essential. Coughing and expectoration are encouraged. Results are dependent upon understanding and cooperation of patient. Automatic carry-over should begin at about Exercise 3.

The experience in 2 patients is worthy of description.

Case Reports. CASE 1. An active man of 54, in charge of advertising in the War Department, came to see us because of a severe cough and progressive respiratory distress following so-called "virus pneumonia." He was most uncomfortable, had given up golf, was unable to walk a city block without discomfort and was applying for retirement. He had emphysema and his chest expansion was about one-half inch, his respirations were labored, his diaphragm was low and his breath sounds were barely audible. Roentgenograms revealed a flat and low diaphragm and overventilated lungs. On fluoroscopy and during forced expiration no trapping was noted. Bronchoscopy showed a normal bronchial tree. It was thought inadvisable to make bronchograms. His vital capacity was 1.2 liters and the anticipated capacity was 3.6 liters. The maximum breathing capacity was reduced. Instruction in the exercises was followed by dramatic improvement within 2 weeks. His vital capacity rose to 3.2 liters and the maximum breathing capacity increased somewhat. In fact, 4 weeks after instruction had been instituted, he played 9 holes of golf without much respiratory distress.

CASE 2. A 61-year old statistician from Philadelphia had noted progressive respiratory distress for a period of about a year. His symptoms became greatly exaggerated following an attack of bronchitis 7 weeks before his admission to the hospital in May, 1951. He had a severe cough, productive of only scant amounts of a glary mucoid sputum. He had lost weight. His exercise tolerance was nil, in fact, he was bed-ridden. The thorax was of the emphysematous type: the diaphragm was low and there were many squeaky rales throughout both lungs. The chest expansion was about ¾ inch from full expiration to full inspiration. The roentgenogram revealed clear lungs with a small heart and a flat diaphragm. Fluoroscopy showed free movement of the diaphragm. The bronchoscopic examination did not disclose any intrinsic bronchial disease. He was treated with bronchial dilators, expectorants and sedatives. He was given his first instruction in respiratory exercises on his fourth hospital day and he carried them out during his 10 weeks' stay in the hospital. Not only was there an increase in his vital capacity from 1.6 to 4.2 liters and an increase in his maximum breathing capacity, but there occurred striking changes in the blood count and blood composition. The hematocrit fell from 54.2 on admission to 44, and there was a comparable reduction of the hemoglobin from 17 to 15 gm. Perhaps the change in CO_2—combining power is not striking but in this 10-week period it fell from 38.4 to 28 mEq./L. This is the only patient in our series in whom these changes have been observed. When seen recently, he was moderately active with-

out distress. He was using the newer type of respiration most of the time and we have even observed this while he has been asleep.

Discussion. There is nothing new in using respiratory exercises to treat emphysema. Thomas[11] emphasized, as have Christie[2,3,4] and others[5,10,12], that the important phase of respiration in the emphysematous patient is expiration. Christie and others felt that this effort would be of necessity an unnatural effort. However, it is our opinion, indeed, our experience, that it can be developed into a natural effort, by systematic and persistent instruction in the series of exercises here presented.

Summary. There are described a group of respiratory exercises which have been found to be a very useful adjunct in the treatment of emphysema.

We are indebted to Miss Mirian E. Miller, R.P.T., supervisor of the Physical Therapy Department of the Johns Hopkins Hospital, for her cooperation and for the description of the exercises.

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COMPARATIVE STUDY OF ASCORBIC ACID LEVELS IN GASTRIC SECRETION, BLOOD, URINE AND SALIVA. II. SATURATION STUDIES*

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There may be several origins for the ascorbic acid in gastric juice. It may be a secretion participating in, or resulting from general or specific metabolic activity of certain or all gastric mucosal cells. It may be a gastric cellular excretion. Some could be a residuum incidental to dietary intake. All three possibilities may contribute to the total gastric juice content. This study was undertaken to determine the effects of one factor, ascorbic acid saturation, on the gastric juice levels.

In normal individuals, the vitamin C in the gastric secretions did not parallel the whole blood levels. It was suggested that the former "probably represents a function of the gastric cells. Whether all of the gastric mucosal cells are involved in this mechanism, or only specialized ones, has not as yet been determined"[8]. The amount of free and total gastric acid seemed to have no constant relationship to the gastric ascorbic acid content, except possibly when other gastric cellular activities were depressed. This relationship has been indicated by others[6].

There are various ways of influencing the ascorbic acid level in the blood. Vitamin-C intake may vary over a wide range with proportional whole blood level changes. Absorption of ascorbic acid is altered by gastric infection, pathologic processes in the small intestine from which it is normally absorbed[24], and by gastrointestinal hypermotility[15]. Excretion by the skin, colon and particularly the kidney with its Tm for ascorbic acid[7] are parts of the regulatory control of body concentration.

Other nutritional elements may affect blood ascorbic acid values. With increased protein intake, there is increased ascorbic acid excretion and reduced blood concentration[1]. This relationship has been cited as contributing to scurvy in individuals whose diet, not scorbutogenic of itself, was made so by high protein intake. There is a relationship between factors controlling blood cholesterol, progesterone and ascorbic acid[2]. Other metabolic mechanisms, such as osteoid matrix formation and possibly calcium mineralization, are related to ascorbic acid utilization[4].

Both chemical and endocrine influences play important roles in fluid, tissue and total body reserves of the vitamin. Steroid production[9], insulin[17] and pregnancy[2] indicate the close cor-

* Supported by a grant from the United States Public Health Service.

relation of ascorbic acid metabolism to many general physiologic processes. In pregnancy, the vitamin C-storing corpus luteum and its progesterone production are associated with elevated blood and urine ascorbic acid levels. Adrenocorticotrophic hormone, cortisone and epinephrine raise blood levels, increase renal elimination, decrease adrenal cortex stores of the vitamin (and also of cholesterol) and diminish total body ascorbic acid reserves[3,5,13,18,19,20].

Other conditions which influence blood ascorbic acid levels are acute and chronic infections, malignancy and other pathologic processes. In acute febrile states, there is a sharp reduction in the body's vitamin C content[11]. In debilitating infections such as active pulmonary tuberculosis[16] and in neoplastic processes, there is progressive depletion. With increasing age, there are lower blood levels[23]. The results are a summation of a variety of influences from inadequate intake to the effects resulting from an abnormal condition.

Neurogenic factors possibly influence vitamin-C levels. It may be inferred from known hormonal effects that there is a relationship between sympathicomimetic states and the mobilization of ascorbic acid. Whether cholinergic or adrenergic stimulation can modify the blood concentration has not been reported. The same is true of gastrointestinal parenchymal values. Studies of gastric juice before and after gastric resection, or before and after interruption of the vagi, would settle this important point. Interpretation in the light of the effects of adrenocorticotrophic hormone on gastric cellular secretion as has been reported for gastric acids[10] may help to clarify this phase of the end-results of ascorbic acid metabolism. It may help to correlate hormonal, neurogenic and vitamin influences by a quantitative physiologic method.

It is possible, then, that the many potential agents which control the blood ascorbic acid level may apply similarly to the gastric juice content of the vitamin.

Blood levels are more labile than tissue content[12]. Measurement of the former is an indicator of the dynamics by which tissue cells establish equilibria in various forms of metabolism. It has been suggested by Warren that "the amount of ascorbic acid in the plasma may not give a good index of the degree of tissue saturation, and is of little use in showing how much ascorbic acid is used by an individual"[21]. Two points must be made. The first is that ascorbic acid saturation is not necessarily a physiologic state nor indicative of optimum nutrition. This explains the differences in vitamin-C levels in apparently normal persons. The second is that ingested vitamin C probably has to be absorbed into the general body stores prior to utilization, rather than being used directly. Although hypothetical, the importance of this conclusion is evident. The metabolism of this vitamin is related to major body activities, and tissue concentrations are better indicators of total reserves than the fluctuating blood levels.

Various methods for saturating have been used. It has been estimated by Lowry and others[14] that the body contains about 4 gm. of ascorbic acid. For saturation, they gave 2 gm. of ascorbic acid orally in one day, or divided into 4 equal daily doses. They found that the effect of saturation is reflected directly in whole blood and in the content of its various components: plasma, leukocytes and platelets.

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Ludden, Flexner and Wright[15,22] fasted their subjects for 12 hours, gave 1 gm. of vitamin C intravenously and

measured its excretion in the urine at the end of 1½, 5 and 24 hours. An excretion of 450 mg. in 5 hours and 500 mg. in 24 hours was considered normal. These workers noted that it took up to 4 gm. in 4 days to saturate patients in whom the original blood levels were low.

Procedure. Ten normal female medical students on average diets served as subjects (age range 20 to 32 years). On the day preceding the beginning of the saturation study and continuing throughout the 5 days of observation, foods of high vitamin-C content and supplementary vitamins were omitted.

On the first day, control ascorbic acid determinations were made on blood, urine, saliva and gastric juice, using the methods described in a previous report[8].

Five hundred milligrams of ascorbic acid were administered orally to each subject daily for 4 days. Ascorbic acid determinations were made on 24-hour urine samples every day of the series. A blood level was determined on the 3rd and 5th days. In several cases, blood levels were done 3 to 5 days after the final ascorbic acid administration.

Results. BLOOD. All except one of the subjects for saturation had been included in a previous study for establishing normal values. The average blood ascorbic acid level for this group in 1949 was 1.00 mg. per 100 cc. In 1950, the control before saturation was 1.07 mg. The average for the 2 determinations a year apart was 1.035 mg. as compared with 0.98 mg. for the original group.

After saturation, the whole blood level of vitamin C rose to 1.88 mg. per 100 cc. This was an increase of 81% over the average value of the controls. The pre-saturation blood range was 0.69 mg. to 1.32 mg., rising to a range of 1.44 mg. to 2.8 mg. after saturation. In all of the 10 subjects, there was a rise in the whole blood level, the least increase being 0.345 mg. and the greatest 1.5 mg.

GASTRIC JUICE. The average ascorbic acid level for gastric juice for the subjects in 1949 was 1.01 mg. per 100 cc.; for 1950, 0.764 mg. The average of the two sets of controls was 0.89 mg. According to our previous figures, the normal for this age group was 0.95 mg. After saturation, the average gastric ascorbic acid level was 0.990 mg. Comparison with the 1949 study shows a slight fall in gastric content after saturation. Comparison with the 1950 figures showed a 30% increase. Compared with the 2-year average, there was a rise of 11%. This probably represents an approximation of the effect of saturation.

SALIVA. The salivary content of ascorbic acid in the 9 subjects done in 1949 was 0.094 mg. per 100 cc. The 1950 group averaged 0.08 mg. The average of the 2 pre-saturation series was 0.0865 mg., as compared with our standard salivary level of 0.07 mg. The range was 0 to 0.372 mg.

After saturation, the salivary ascorbic acid concentration was 0.089 mg. with a range of 0.007 to 0.213 mg.

From these figures, it can be seen that there was no appreciable effect

TABLE 1.—ASCORBIC ACID LEVELS BEFORE AND AFTER SATURATION

	Controls			*Pre-Saturation Range*	*Post-Saturation Average*	*Post-Saturation Range*	*Per Cent Increase*
	1949 mg./100 cc.	*1950 mg./100 cc.*	*Average mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	
Blood	1.00	1.07	1.035	0.69 – 1.32	1.88	1.44 – 2.8	+ 81
Gastric Juice	1.01	0.764	0.89	0.042 – 3.66	0.99	0.287 – 2.97	+ 11
Saliva	0.094	0.08	0.0865	0 – 0.372	0.089	0.007 – 0.213	+ 0
Urine Concentration	1.25	1.80	1.52	0.75 – 4.50	28.91	16.1 – 45.0	+1800
Urine Excretion	11.65	16.79	14.22	6.30 – 41.4	319.0	226.0 – 434.9	+2143

on salivary vitamin-C concentration by body saturation.

URINE CONCENTRATION. The 1949 series of subjects had an average urinary concentration of 1.25 mg. per 100 cc. In 1950, the average was 1.8 mg., the average of the 2 pre-saturation studies being 1.52 mg. The pre-saturation range was 0.75 to 4.50 mg. The average for normal subjects as reported originally was 1.50 mg., which is a close correlation considering the numerous possibilities of error in the collection of specimens, the character of the diet, racial differences and cyclic modifications.

After saturation, the urine vitamin-C concentration rose to 28.91 mg., an increase of 1800%. The post-saturation range was 16.10 to 45.0 mg.

URINE EXCRETION. The average 24-hour excretion of vitamin C has been shown to be 14.15 mg. The average excretion for the 1949 group was 11.65 mg. in 24 hours. In 1950, the average 24-hour excretion was 16.79 mg. The average of the 2 pre-saturation values was 14.22, with a range of 6.30 to 41.4 mg.

After saturation, the average urine excretion was 319.0 mg. in 24 hours (range 226.0 to 434.9 mg.). This is an increase of 2143%. The average ascorbic acid retention of the load dose was 42%, with a range of 26% to 59%. These figures were obtained by subtracting from 2000 mg. (the amount of ascorbic acid administered) the total amount excreted during the 4-day period minus the subject's normal ascorbic acid excretion over the same period. In one case, the subject had returned to her normal level in 7 days, in another in 9 days.

GASTRIC ACIDITY. In the 1949 series, the average free hydrochloric acid in the gastric juice was 9.88 clinical units (range 0 to 38.5) and the average total gastric acid, 24.33 clinical units (range 7.2 to 54.5). A year later, the figures were 8.3 clinical units of free acid (range 0 to 20.2) and total, 19.9 clinical units (range 6.2 to 33.0).

After saturation with ascorbic acid, the average free hydrochloric acid in the gastric juice was 7.63 clinical units, with a range of 0 to 19 clinical units. There was a fall of 23% compared with 1949, and of 8% compared with 1950. After saturation, the total gastric acid was 17.12 clinical units, with a range of 3.75 to 30.7 clinical units. This is a drop of 29% (1949 figures) and 14% (1950) figures.

Summary. A study of 10 normal female subjects was made in 1949 and in 1950 for concentration of ascorbic acid in whole blood, gastric juice, saliva and urine. Determinations were also made of the 24-hour urine excretion of the vitamin. These figures and the 2-year average were compared with a large series in which standards of normality had been determined. The close correlation corroborated the methods and the results.

These subjects were given 2 gm. of ascorbic acid orally in equal doses over 4 days as a saturation procedure. This amount is about one-half of the body's normal reserves.

It was noted that:

1. The average whole blood ascorbic acid level rose from 1.035 mg. per 100 cc. to 1.88 mg., an average increase of 81%.

2. The average gastric juice concentration of ascorbic acid rose from 0.89 mg. per 100 cc. to 0.99 mg., which is an average increase of 11%.

3. The urine concentration rose from 1.52 mg. per 100 cc. to 28.9 mg. During the 4-day test period, there was an average 24-hour excretion of 319 mg. The average ascorbic acid retention was 42%.

4. There was no appreciable change in the salivary ascorbic acid concentration after saturation.

5. Both the free and total gastric acid levels were lower after ascorbic acid saturation, the former falling an average of 16% and the latter 22%.

Conclusions. After saturation, ascorbic acid levels in the blood and the amounts excreted in the urine are in direct proportion to the intake, representing simple *quantitative* balances. Tissue content, as measured by gastric juice and salivary concentration, rose far less proportionally and may represent a *qualitative* change in which cell function is involved. Such levels reflect temporary fluctuations in total body stores. The saturation values do not persist and the average falls to the individual's level within a few days. This explains why, in normal subjects, there is a variation of the vitamin concentration in spite of identical intake without signs of biochemical or clinical deficiency.

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EXPERIMENTAL RHEUMATIC CARDITIS, PERIARTERITIS NODOSA AND GLOMERULONEPHRITIS

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IN the past 50 years, a considerable amount of animal experimentation has been done in which lesions have been produced that have been compared to those occurring in human cases of rheumatic carditis, periarteritis nodosa and glomerulonephritis. As will become evident from the review of the experimental literature to follow, the lesions of interest from the point of view of all three diseases have been produced in the same or similar experiments. It is from this coincidence of experimental lesions that the diseases are grouped together for the purpose of this review rather than from any common association of the conditions as they occur in man. It is superfluous to state that the definitive etiological and pathogenetical factors concerned in the production of rheumatic fever, periarteritis nodosa and glomerulonephritis are still not understood and that interest in the experimental work arises from its possible bearing on these problems. The experimental studies have been made possible by the existence of a fairly complete and specific body of clinical and morphological facts which form the basis of comparison with the experimentally induced diseases. However, this review will be principally concerned with a consideration of the literature on the morphology and pathogenesis of the experimental lesions. It will not constitute a complete survey but rather an attempt to present a concise account of the present status of the field with particular emphasis on the lesions produced by foreign proteins.

Lesions of the Heart. (a) THE CARDIAC LESIONS IN RHEUMATIC FEVER. A peculiar lesion of the heart in human rheumatic fever was first brought into prominence by Aschoff in 1904[6], who described its basic characteristics, although he credited Romberg with its discovery the year before. Since that time numerous investigators have confirmed the fact that the lesion which

came to be known as the Aschoff body was specific for rheumatic carditis[27], [27a,28,52,52a,145]. The presence of multinucleated giant cells was noted by Aschoff[6] but it remained for Gross and his co-workers to describe the fact that it was the abundant basophilic cytoplasm with ragged margins that was the distinguishing feature of the Aschoff cells[52], since the nuclei were similar to Anitschkow myocytes that could be found in the hearts of normal men and animals[26a,37]. Aschoff[6] also described the amorphous eosinophilic material in the lesions. Klinge[72a] maintained that this material was the product of degeneration of collagen which, in the process of degeneration, acquired the tinctorial properties of fibrin ("fibrinoid necrosis" of collagen). Recently, however, the concept that the material is derived from necrotic myocardial fibres has been revived[104]. Variations in the structure of the Aschoff body were subsequently described by Gross and Ehrlich[52a], who also correlated the appearance of the cardiac lesions with the clinical course of rheumatic carditis. Pathological changes in the remainder of the body, in which the fibrinoid necrosis is prominent, have been described by numerous authors and because of this characteristic, the disease has been grouped with others, such as lupus erythematosus, dermatomyositis, rheumatoid arthritis and periarteritis nodosa under the term "diffuse collagen diseases"[1,11,34,34a,70,71,121,144].

(b) Experimental Lesions of the Heart in Animals. It was against the background of the well-studied morphology of rheumatic fever that experimental studies were made. The first attempts to reproduce the heart lesions of rheumatic fever consisted of the injection of bacteria, including streptococci, non-hemolytic[16,26,27,28,57,64,85,111,116,135,145a,154] and hemolytic[26,55,64,68,107,126,126a,126b] and other bacteria[94] isolated from rheumatic patients. Most of the experiments employed the intravenous route of injection and gave rise to lesions like those of subacute bacterial endocarditis in man and non-specific lesions of the myocardium that did not conform to the criteria of rheumatic carditis[51a,57,126,126b,145a]. The injection of tissue extracts and fluids from patients with rheumatic fever also failed to induce typical lesions in animals[57a,97].

Among the first to demonstrate that lesions of the heart could occur in association with anaphylactic sensitization of animals to foreign proteins was Longcope in 1915[88a], who sensitized rabbits with horse serum and egg albumin. Some years later, Klinge[72] produced lesions in the hearts of rabbits which he considered to be the counterpart of the lesions of human rheumatic carditis, by sensitizing rabbits with repeated subcutaneous injections of horse serum followed by a larger dose into one or both knee joints. He was followed by a succession of investigators who injected various foreign proteins: horse serum[2,3,18,33,38,45,61,73,88,88a,94,95,98,99,124a,124b,126a,147,157] or its fractions[126b,128,157]; bovine serum[58,96] or its fractions[58,102]; egg albumin[88,88a,94,95,126b,128]; pork serum[65,73] and duck serum[38]. Many investigators employed subcutaneous sensitization[3,18,65,72,73,147] followed by one[147] or more[18,147] intravenous injections of serum or intra-articular injections[72,147]. However, more recently it has become common practice to sensitize and challenge with massive intravenous doses of antigen[38,45,58,61,99,101,107,124,124a,124b,157]. Others have combined the foreign proteins with killed bacteria[98,126,126a] or have incorporated them in adjuvant mixtures[98] designed to enhance their sensitizing ability. Exposure to cold[74,150] and muscular exercise[73] have also been employed in conjunction with serum administration. By whatever

means of sensitization employed and with nearly all the antigens, lesions of the myocardium and heart valves have been produced and the chief point of controversy has been the degree of similarity of the experimental lesions of the heart and its valves to those of rheumatic carditis. Nearly all investigators have recognized a similarity, but most have regarded them as not identical with the lesions of the human disease[6,6a,6b,33,72,98,102,124c,147] but rather as having a "similar reaction pattern" or as being "Aschoff-like"[38,61,99,124,124a,124b]. A few have accepted the lesions as typical Aschoff bodies[72,107]. On the other hand, the similarity of the lesions to spontaneously occurring lesions in the hearts of animals[51,84,97a] has been pointed out[3,98,99,102]. The experimental lesions occurring in hearts already the seat of periarteritis nodosa of small coronary arteries were difficult to distinguish as separate lesions in many instances[98].

The opinion has also been expressed by some authors that the lesions of the heart resemble most strongly the lesions seen in human serum sickness[24,36] or sulfonamide allergy[100]. It is clear from a perusal of the literature that those who are cautious in their interpretation, or who deny the identity between experimental and human lesions, outnumber those who consider the lesions identical. The lack of identity between the lesions has been attributed to variation in the response of different species[124a], but it has also been pointed out that such an assumption is one that requires to be proved[51a]. Substantiation of the last statement may be derived from the work of Murphy and Swift[105,105a] who have produced typical Aschoff bodies in the hearts of rabbits by means of repeated intracutaneous infections with Group A hemolytic streptococci.

Lesions of the Arteries. (a) Periarteritis Nodosa in Man. Periarteritis nodosa was first described in 1865 by Kussmaul and Maier[77]. Since that time sporadic cases have been reported, which have been extensively reviewed and analyzed[4,75,86]. It is evident from the reviews and numerous individually reported cases that the lesions vary from case to case and that their morphology was comprehensible only by considering the disease as a process with many stages. The pathogenetic sequence of events has been well described by Duff[34,34a] and Arkin[4] from which it is evident that no single feature, such as periarterial inflammation, or fibrinoid necrosis of the connective tissue, may not necessarily be present in all cases, but that it is characterized by the tendency to involve the arteries in a segmental fashion and would hence be better termed "polyarteritis nodosa". All coats are involved in what is at first a necrotizing process with acute polymorphonuclear and eosinophil exudation. However, the cells of the exudate soon become predominantly mononuclear and the necrotic portions of the artery proceed to healing with fibrotic thickening of all layers of the arterial wall.

(b) Experimentally Induced Arterial Lesions. Experimentally, lesions identical with the lesions of periarteritis nodosa in man have been produced in animals. In experiments employing foreign serum protein in rabbits[45,58,72] arteritis occurs in conjunction with the myocardial lesions already referred to. In fact, the lesions of the arteries are the more prominent of the lesions occurring in these experiments. The experimental arteritis has been seen in acute, subacute and chronic stages, comparable in every way to the lesions of the arteries occurring in human cases of periarteritis nodosa and are so accepted by nearly all observers, although some of the later or chronic stages have been compared to the sclerotic types of lesions occurring in

the arteries in lupus erythematosus[124c].

Apart from the massive administration of foreign serum proteins, lesions like those of periarteritis nodosa have been produced in rats by the administration of desoxycorticosterone acetate[133,134] and also by wrapping the kidneys of rats in silk[139,140,159] or cotton[29], in order to produce hypertension. However, in connection with the arterial lesions in rats, it should be noted that they have been observed to occur in as florid a manner in older rats not treated in any way[155], which makes it difficult to evaluate their occurrence as a result of experimental treatment. Spontaneous lesions of the arteries of rabbits have been described in the coronary arteries[98], but they are sufficiently different from the experimental lesions of periarteritis nodosa that they can be easily differentiated. Attempts to differentiate the type of arteritis occurring in rats from those produced by sensitization of rabbits to foreign proteins or human lesions, so called "hypersensitivity angiitis",[140] have not been very convincing. In rabbits treated by wrapping the kidneys in polyethylene cellophane[69], periarteritis nodosa was observed to occur in association with infection about the operative site. Hypertension was not always present in association with the development of the lesion in rabbits[69] as had been suggested to be necessary in the experiments with rats[140].

Lesions of the Kidneys (Glomerulonephritis). (a) HUMAN GLOMERULONEPHRITIS. Almost 150 years ago Wells[153] and Plenciz[115] observed "blood and serum" in the urine of patients with post-scarlatinal "dropsy". The gross morphological picture of glomerulonephritis was established by the classical work of Bright in 1827[17] and the histological findings by Langerhans in 1879[79]. However, the correlation between the clinical and pathological findings has been a matter of confusion for many years. The classification of renal disease by Volhard and Fahr[148] is the one most generally employed and is based on the location of the lesions in the nephron. These authors clearly differentiated "diffuse glomerulonephritis" from other affections of the glomeruli of the kidneys. Much more recent work has been done by Bell[7,7a,7b] and McGregor[106,106a] and by Ellis[39] to establish a correlation between the clinical and pathological findings. It has been pointed out by these investigators that glomerulonephritis is a diffuse disease of the kidneys involving nearly all or all of the glomeruli with no tendency to segmental arrangement or focal involvement of isolated glomeruli. The lesions are further characterized by a proliferative activity on the part of the endothelial and epithelial cells of the glomerular tuft and Bowman's capsule. The former leads to obliteration of the capillary lumina and the latter to the formation of the characteristic epithelial crescents. Marked thickening and splitting of the basement membrane of the glomerular capillaries is also characteristic of the disease. According to the clinical history and the state of the lesions at necropsy the disease has been divided into the acute, subacute and chronic stage[7,7a,7b], extracapillary or intra-capillary types[148] or Type I and Type II nephritis[39]. While there is some argument as to the exact clinico-pathological correlation of the various stages, the general morphological picture is fairly well agreed upon by most observers. Not so with etiological or pathogenetical factors, where many theories have been advanced with more or less basis in fact.

(b) EXPERIMENTAL GLOMERULONEPHRITIS. (1) *Bacterially-induced renal lesions.* Attempts have been made to induce glomerulonephritis in animals by repeated intravenous injection of

living bacteria, such as: *Streptococcus viridans*[8,9,35,35a,40,59,74,76,81,83,94,112a], *Streptococcus hemolyticus*[9,55,59,112a], *Staphylococcus pyogenes*[32,40,94], B. coli[40,94], Pneumococci[15], *Brucella suis*[92] or with autolysates of the organisms[15,35,120], their toxins[35,35a] or filtrates[123]. In some experiments, organisms were injected directly into the renal arteries[25,32,89,90]. Most of these experiments were performed on rabbits[9,15,25,35,40,59,83,89,94,112a,120,123,139] but mice[76], monkeys[8,55,139], dogs[68,92] and guinea pigs[13] have also been employed. Despite the many claims that the ensuing lesions were quite comparable with human glomerulonephritis[32,35,59,76,123], either the illustrations were unconvincing[15,35,40,59,76,90,92] or the authors themselves described glomerular involvement that was not generalized and which could better be regarded as a focal glomerulonephritis or pyelonephritis[25,68,83,89,92]. Horn[62] and Leiter[83], who reviewed the literature on this phase of experimental glomerulonephritis came to the same conclusion. The earlier experimenters, therefore, had some difficulty in distinguishing the lesions they obtained from pyelonephritic lesions that occur spontaneously in the kidneys of rabbits and guinea pigs[112]. There is only one report in the literature in which a spontaneous glomerulonephritis of the diffuse proliferative type is described in rabbits[91] and it is doubtful if the reasoning employed to establish the lesions as spontaneous can be accepted. Furthermore, most investigators, who have studied large numbers of rabbits, have denied the existence of spontaneous diffuse glomerulonephritis. There are only 2 possible exceptions in the literature in which the lesions produced by the injection of living organisms might be regarded as true glomerulonephritis. One is in the study of Masugi and Isibasi[94], in which some of the glomerular lesions taken individually show a considerable amount of endothelial proliferative activity. The second is found in a single monkey among many injected by Bell and Clawson[8]. In reports of experiments with bacteria, and no matter what the nature of the glomerular lesions produced, it is frequently noted that the damage to the kidneys was more marked after repeated injections and after vaccine sensitization than after single injections. Some authors have therefore suggested that sensitization of the animals was important in the pathogenesis[25,89,94].

(2) *"Nephrotoxic" nephritis.* Since 1900, there has been continued interest in "cytotoxic sera", among which nephrotoxic sera aroused particular enthusiasm because they appeared to have a specific damaging effect on the kidneys of animals into which they were injected[87]. The earliest experiments employing nephrotoxic sera were of two types. The first of these employed an iso-nephrotoxic serum that was prepared by injecting an emulsion of kidney from one species into another animal of the same species. The serum from this animal was then injected into another animal, again of the same species[110,113]. This procedure was found to be without specific effects on the kidneys. The second type of experiment employed a heterologous nephrotoxic serum that was prepared by immunizing animals of a second species to kidney tissue of the first. The immune serum thus obtained was injected into an animal of the first species. The first experiment employing sera prepared in this way[87] produced rather equivocal renal changes, such as fatty degeneration of tubules[87,113a], hyperemia of the medulla[158] and glomerular capillaries[110], bloodlessness of glomeruli[13a], thrombosis of glomerular capillaries[113,156], and casts in the tubules[87,110,113a,156]. Albuminuria, hem-

aturia and cylindruria were observed to occur following the injections and just prior to death several animals were thought to have died in uremia[87,110,113,113a,156,158]. The early authors commented on the marked hemolytic and hemagglutinative properties of the sera. In the early experiments, washing of the kidneys was ineffective in abolishing these properties and, perhaps for these reasons, the experiments were of short duration, the animals dying of the "toxic" effects of the sera within a week or two of the injections. Interest in nephrotoxic sera was revived by Masugi[93], who described changes in the glomeruli in rats which were injected with rabbit anti-rat-kidney serum. The serum was produced in rabbits by injection of emulsified rat kidneys which had been cleansed of blood by first perfusing the entire rat through the thoracic aorta. The sera so produced showed minimal hemolytic and hemagglutinative properties and variable precipitating ability against rat kidney extracts. Some of the sera showed a greater ability to precipitate extracts of other organs, such as liver, than extracts of kidney. It was obvious, therefore, that the effects on the kidney could not be regarded as purely the effect of the specific anti-kidney activity. Lesions were observed by Masugi[93] within 24 hours consisting of swelling of the capillary tufts due to hyperemia and stasis in the loops, hemorrhages into the glomerular capsules, and hyaline thrombosis of some of the capillary loops. Within 3 days he observed thickening of the walls of the capillaries by fibrin deposition and proliferation of endothelial cells; tubules were distended with albuminous material. In a further study, in which anti-rabbit-kidney duck serum was injected into rabbits[93a] a definite albuminuria appeared within 4 to 8 days of the first injection with hematuria and cylindruria. Good illustrations of the lesions indicated that there was endothelial and epithelial proliferation in the glomerular tufts with crescent formation in many instances in 29 to 40 days. These changes were generalized and were identical with the lesions of human glomerulonephritis. Weiss[152], Gukelberger[54], Hemprich[60] and Arnott and associates[5] confirmed the production of glomerulonephritis with anti-rabbit-kidney duck serum in rabbits and showed that the disease could progress to a chronic form in 50 to 75 days. Subsequently a similar nephritis was produced in rats with anti-rat-kidney rabbit serum[41,130,136,137,137a,138,143]. Glomerulonephritis has also been produced in rats with anti-rat-placenta rabbit serum[130].

The dose of anti-kidney serum administered to animals amounted to about 10 to 20 cc. per kilo of body weight, administered in divided doses for 3 successive days[5,60,93a,130,136,137,137a,137b,138,143]; in only exceptional instances was a further dose administered at a long interval after the first course[93a]. Most authors have thought that the lesions resulted from a reaction between the injected anti-kidney antibody and the kidney substance of the host and regarded the reaction as an allergic one. However, the effect has also been regarded as "toxic" in view of the fact that lesions may be elicited after one injection of a very small dose[152].

Recently, experiments have been performed in which extracts of rat kidney have been injected into rats combined with the bodies of killed and dried beta hemolytic streptococci[21,21a,21b]. It was reported that glomerulonephritis had been produced in these animals and that auto-antibodies to kidney had been demonstrated in the blood. However, the lesions illustrated were not convincing, nor were the results confirmed in either rats[63] or rabbits[114].

(3) *Glomerulonephritis induced by "normal" foreign proteins.* Many studies have now appeared, in which a glomerulonephritis has been produced by massive injections of foreign serum or other foreign proteins. In many of the experiments, cardiac lesions and lesions of arteries were also produced[38,58,88,98,101a,102,124a,151,157], but in some cases glomerulonephritis has been produced in the absence of arterial or heart lesions[109]. Many antigens have been used: egg albumin[88], horse serum[88,98,124a], fractions of horse serum[157], bovine serum[58], bovine gamma globulin[58,101], bovine albumin[58]. The dosage employed was high, being about 10 to 20 cc. of serum per kilo of body weight[38,98,102,124a,157] or about 1 gm. of the more purified proteins[88,101]. This quantity of serum was given usually on two occasions with an interval of 10 to 17 days between them, but some investigators have given smaller doses at more frequent intervals over longer periods of time[88,109]. Lesions have also been seen following a single injection[58]. The glomerulonephritis that has been produced by these methods is of varying severity. In some studies, the lesions that have been described were of minimal severity but still showed a generalized endothelial and epithelial proliferation of the glomerular epithelium. However, the injection of bovine gamma globulin on two occasions into unilaterally nephrectomized rabbits has allowed the production of florid lesions, characterized by epithelial proliferation, thickening of the basement membranes of the glomerular loops and epithelial crescent formation. The concomitant formation of casts with associated atrophy and dilatation of tubules, give an appearance identical to that of human glomerulonephritis[101]. Florid lesions have also been produced by the addition of killed and dried streptococci to intravenously injected antigens, by incorporating the antigens in Freund's adjuvant[98], or by exposing the animals to cold during the experimental period[74,101a].

Comparison Between "Nephrotoxic and "Normal" Protein Nephritis. The lesions produced by nephrotoxic sera[5,93,93a] and by non-nephrotoxic (normal) foreign proteins[58,88,101,109,124a,151] are similar in their histological aspects. Although the opinion has been expressed that there are some differences in their histological characteristics[44a], there is little doubt that the lesions of both types of experiments are very much the counter parts of the lesions seen in cases of glomerulonephritis in man. Furthermore, albuminuria, hematuria, cylindruria and occasional deaths in uremia have been recorded in association with both types of lesions. In addition to having an identical behavior, it is important to recognize that both types of lesions were produced by intravenous injection of proteins heterologous to the species of animal in which the lesions appeared. However, the mode of administration was distinctly different. Repeated injections of nephrotoxic sera usually were given during the first 3 or 4 days of the experiments[5,60,93,93a,138,152]; in only exceptional instances were repeated doses given at longer intervals[93a]. Lesions have been produced with a single dose[152]. On the other hand, the normal serum proteins usually were injected at least twice at an interval of 10 to 17 days. In animals of both types of experiments, anaphylactic type of hypersensitivity to the injected serum was demonstrated to develop ultimately. This has been demonstrated by the presence of precipitin in the blood and positive skin tests to the injected antigens by almost all the investigators. Albuminuria has been reported to occur within a few hours[41,137] on the first to third day[152], on the 4th

to 8th day after the first injection of nephrotoxin[93a], or on the 5th to 9th day[60]. However, the earliest albuminuria appeared as a trace or minimal quantities and the major amounts of albumin began to appear from the 8th to 11th days. The situation parallels that seen after the first injection of bovine gamma globulin[151] or of horse serum[74]. The time of development of albuminuria corresponds to the time at which precipitating antibodies can be detected in the blood[151]. The latent period in the development of experimental lesions brings to mind the commonly described interval between scarlet fever and the development of acute glomerulonephritis in patients[148]. Thus far no one has been able to prove definitely that the site of development of the lesions resulting from the administration of normal sera is the place at which the antibody-antigen reaction takes place, although several attempts have been made[75,80,103]. However, by labelling with radioactive elements, it has been shown that anti-mouse-kidney rabbit serum localized itself to the glomeruli of the kidney of the mouse[50] and anti-rat-kidney rabbit serum to the glomeruli of rats[117,118] when injected intravenously, while anti-sera prepared against other tissues or normal sera injected on one occasion do not become so localized[117,118,119]. Thus, although nephrotoxic nephritis has many things in common with glomerulonephritis produced by multiple massive injections of normal sera, it may be that the nephrotoxic sera containing anti-kidney antibodies tend to localize themselves in the kidney immediately, but the normal sera require the development of antibodies in the body of the host which react in various sites of the body, heart, arteries and glomeruli, to produce their pathological effects. This may account for the fact that arteritis and carditis are not described in association with nephrotoxic nephritis.

However, there are several discordant facts to be explained in this interpretation, such as the fact that the production of nephrotoxic nephritis is not necessarily proportional to the titer of anti-kidney antibodies in the serum[93a,130,136] and indeed, the nephrotoxic sera may be shown, in some instances at least, to contain more activity against other organs, for example, liver[93a] or placenta[130] than against the kidney substance. Antigen-antibody reaction, if it occurs, in the production of the lesions is not by itself responsible for the lesions, since it has been pointed out that injecting kidney extract just prior to the injection of anti-kidney serum will inhibit the development of glomerulonephritis in rats[136]. This implies a reaction between antibody and antigen within the body without development of renal lesions. Furthermore, the simple production of anaphylactic shock does not induce similar lesions of the kidney[46,46a,127,127a,127b], nor do lesions develop in all animals similarly sensitized[2,3,18,38,45,58,61,65,72,73,88a,94,95,98,99,101,102,107,124,124a,124b,124c,147,157].

Pathogenesis of Lesions Induced by Foreign Proteins. (a) *State of hypersensitivity.* It is exceptional to find an investigator who does not believe that lesions produced in animals by administering foreign sera are allergic in origin[153], but, as may be deduced from the above discussion, there has been little proof that the association of anaphylactic hypersensitivity with the occurrence of lesions of the heart, arteries and kidneys is more than coincidental. Attempts to correlate the development of lesions with the titers of antibodies in the blood[101,124a,136] or with the intensity of skin reactions[124a] have yielded equivocal results. Attempts have been made to inhibit the lesions of the heart, arteries and kidneys with agents known to inhibit antibody formation. In this connection, the action of salicylates[23,44,125,141,142], anti-

histamine drugs[23,78,125], nitrogen mustard[19,50,129], Roentgen-rays[19,67,129] and miscellaneous drugs[23,44,50] have been studied in an attempt to inhibit the occurrence of lesions. Conflicting claims have been made, but it is evident from the results that no clear-cut inhibition, that could stand statistical evaluation, has resulted from the use of these agents. However, using nitrogen mustard, an inhibition of lesions was reported[30] which was said to be correlated with a threshold level of antibody formation[19]. These studies have not been confirmed[50,74]. Kay[67] reported an inhibition of nephrotoxic nephritis by total body irradiation of rabbits, which coincided with a diminution of the precipitin titer, but this too has been denied[20]. Recently, it has been reported that nitrogen mustard and Roentgen-rays inhibit the formation of globulin glomerulonephritis in rabbits and that this is associated with a failure of the complement titer to observe the variations that usually occur in the animals that develop glomerulonephritis[129]. This result requires confirmation.

It has also been suggested that the reason for the development of the lesions of the heart, arteries and kidneys in animals treated with whole serum might be a function of the complex physico-chemical composition of the proteins contained in whole serum and that each lesion might develop from a different protein component of the injected serum[58,61]. However, experiments utilizing purified fractions of bovine serum[58,74,101,102] or relatively pure fractions of horse serum[157] have not substantiated this theory. Any tendency of a particular protein to produce a given lesion was only on a very superficial plane.

The failure to demonstrate a constant correlation between the antibody titers, or the intensity of skin tests with the occurrence of lesions; the lack of confirmation of a relationship between specific proteins and the occurrence of lesions; along with the observation that a moderate reduction in total food intake will inhibit the formation of antibodies and the occurrence of experimental globulin glomerulonephritis has led to the suggestion that it may not be the actual level of antibodies in the circulation that is correlated with the lesions, but rather a question of the rate of "turnover" or metabolic production and destruction of antigen and antibody that may be of importance[151]. This suggestion is worthy of further experimental consideration in view of the conclusion of most of the authors in the field that the lesions are associated with the state of hypersensitivity and in view of the equivocal nature of the evidence so far at hand.

(b) *Role of endocrine glands.* The discussion of the pathogenesis of the lesions would not be complete without a discussion of the possible role of the adrenal. In his discussion of the "General Adaptation Syndrome", Selye[132, 132a,134] included the lesions produced by foreign proteins in animals as a manifestation of the result of exposure to non-specific "stress". Attempts have been made to correlate the occurrence of the lesions with alterations in metabolism that have been described as part of the "general" adaptation syndrome". Variations in the serum sodium, serum chlorides and sodium to chloride ratios have been shown not to be related to the development of lesions[74,108], nor does the blood sugar vary in such a manner as to provide evidence that the mechanism envisaged by Selye is of importance[98a]. Changes in the weight of pituitary, adrenal and thymus glands can be shown as a result of cold and serum administration, but these are not correlated with the occurrence of lesions similar to those produced by foreign serum proteins[98a]. Furthermore, the exposure of rabbits to cold alone does not produce lesions similar to

those seen after anaphylactic sensitization to large doses of foreign serum proteins[98a,101a,150]. Thus, positive evidence is lacking for the hypothesis that nonspecific "stress" and the "general adaptation syndrome" is the basis of the lesions.

Recently, attempts have been made to inhibit the development of lesions produced by massive injections of horse serum or bovine gamma globulin in rabbits with ACTH[10,12,23] and Cortisone[122]. These studies, individually, have failed to reveal an unequivocal effect on the lesions. However, when the results of treatment with ACTH and Cortisone are included in the same calculations[10,12,122], a partial inhibition of arteritis and carditis induced by a single injection of horse serum was reported. Since a single injection does not usually produce a high incidence of lesions of heart and arteries and is not a reliable method of producing glomerulonephritis, the results must be considered inconclusive. A suggestive inhibition of the severity of the lesions of the kidneys by Cortisone has been observed by one author[74], while others have reported an inhibition of the appearance of arteritis but not on the glomerulonephritis[109a,131] in experiments in which two massive injections were employed. Cortisone has also failed to inhibit nephrotoxic nephritis in rats[151]. Thus, the effects of treatment with ACTH and Cortisone on the development of lesions of the heart, arteries and kidneys appear to be somewhat inhibitory, but the hormones by no means abolish their occurrence entirely. Even were they to have a complete inhibitory effect, it would still remain to be proved that this inhibition was related to the pathogenesis of the lesions.

Considering that the state of hypersensitivity has some pathogenetical relationship to the occurrence of the experimental lesions, it is interesting to examine the effect of ACTH and Cortisone on the various manifestations of this state induced in animals. A diminution of circulating antibody levels in immunized animals treated with ACTH and Cortisone[14,47,49,146] has been reported along with a decrease in the degree of skin sensitivity of the Arthus type[10,12,48,49,56,131,146]. However, passively transferred antibody levels are not influenced by the hormones[43]. Anaphylactic shock produced in actively immunized animals was diminished in intensity by exposing animals to nonspecific "stress" stimuli[66]. However, no effect on anaphylactic shock was observed by the administration of ACTH or Cortisone in actively sensitized[31,56,82] or passively sensitized animals[42]. On the other hand, the ability of serum to transmit anaphylactic shock passively has been shown to be diminished by both ACTH and Cortisone with the effect of the latter being marked[47]. Thus it would appear that ACTH and Cortisone have an inhibitory effect on the active production of antibodies within the animal body but do not effect the antibody-antigen reaction induced by passively transferred antibodies. The effect of non-specific stress appears similar to the effect of Cortisone and ACTH on anaphylactic shock. This suggests that the changes induced in animals by exposure to nonspecific "stress" may express themselves in an interference with active antibody production.

However, in the absence of clear-cut results with the use of ACTH and Cortisone as inhibitory agents, the absence of other evidence of changes similar to those seen in the "general adaptation syndrome" occurring in association with the development of lesions, and the inability to produce the lesions by non-specific stress alone in rabbits, it is rather difficult to assign an essential

role for this mechanism in the pathogenesis of the lesions produced by foreign proteins.

Summary. The available literature concerning experimental lesions of the heart, arteries and kidneys that bear a relation to the human diseases, rheumatic fever, periarteritis nodosa and glomerulonephritis has been reviewed. It is concluded that the lesions produced in the heart of animals by foreign serum protein sensitization are not identical to those of human rheumatic fever, but that more acceptable lesions have been produced by repeated intracutaneous injections of rabbits with beta hemolytic streptococci. The lesions of the arteries produced by sensitization to foreign proteins are acceptable counterparts of periarteritis nodosa in man. The lesions of the kidneys and the functional changes that occur during sensitization to "nephrotoxic sera" or "normal" foreign sera are also acceptably similar to the lesions of cases of glomerulonephritis in man.

The pathogenesis of the lesions appears to be related to the state of anaphylactic type of hypersensitivity that develops in the animals, but on the basis of the present evidence, this is still an assumption based on close coincidence, rather than on firm proof. It cannot be said on the basis of present knowledge that the "general adaptation syndrome" plays an essential part in the pathogenesis of the lesions.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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PREMATURE BIRTH AS A PROBLEM OF HUMAN POPULATIONS

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PROBLEMS connected with premature births are ordinarily approached by clinical methods, mass evaluation being largely limited to the determination of vital statistics, notably birth, neonatal and infant mortality rates. Application of epidemiologic methods to this field is warranted quite as much as to others, such as geriatrics or adolescence. For infants born prematurely, the gains through prevention or modification of that state are measured in years of productivity[29] and freedom from the crippling handicaps of blindness, palsy and mental retardation. The benefit that follows is in sharp contrast to the lesser advantage of preventive measure at advanced ages, when the profit is so often limited to a few more years of greater comfort.

Premature infants comprise the youngest segment of a population, with its problems chiefly related to underdevelopment and lack of age, just as at the other end of the life span the challenge comes from senescence and the toll of years. A concept of life dating from birth overlooks the usual 9 months of intra-uterine existence with its deaths and its deformities[64,75]; and also such related fields of interest as fertility[73] and birth control[95]. The premature infant is really the bridge between this first period of life and the other seven ages of man.

Even in the absence of congenital disease, the physiologic status of the premature infant is critical[50], for the condition is not so much a morbid process as an abnormal exposure of a potentially normal human being. The fetus is no less a fetus by reason of having been separated from the mother, and the chances for survival are materially less than for the fully developed infant[25,32]. Once expelled from the uterus, the embryo is sure to die as an abortion[40]. While the older fetus may

die as a miscarriage, the chances for survival are better, though the risk of crippling looms large, in inverse proportion to the state of development achieved before premature birth occurs.

Social interest in the premature infant, then, is more than a matter of therapeutics directed towards maintaining life and curing deformity. Concern is with the resulting quality as well as quantity of these youngest citizens. Analysis of the nature and origin of premature birth, and of premature infants as components of a population, has equal importance with the delivery and care of the patient. A better understanding of causative factors, not only as they affect patients but as they affect populations, is requisite to an improved program of control designed to decrease or eliminate preventable deaths and deformities. Thus the challenge of prematurity is no less to the public health disciplines of maternal and child health, epidemology and biostatistics than to the clinical specialties of pediatrics, obstetrics and pathology.

The present purpose is to review available evidence on infants born in a premature state as they represent a phenomenon of human populations. Definitions of prematurity and indices for measurement of the degree of underdevelopment are described. The costs are defined in terms of death, defect and disability. The external environment is examined for features contributing to the frequency of low birth weight. Biological influences inherent in the human host and others associated with pregnancy are considered. The final interest is in epidemiologic studies designed to promote a better understanding of the causes of prematurity and to assess further the late effects of that condition. The aim is toward prevention.

DEFINITION OF PREMATURITY. The question of what constitutes prematurity immediately directs attention to whether judgment is to be based on all infants, or only on those born alive. An omission of stillborn infants has disadvantages[1,85]. The distinction between life and the absence of life at birth is often nebulous and many times depends on the decision of the attending physician or midwife. Local custom and law, in particular burial law[35,87], commonly influence the opinion. A number of causative factors associated with birth of premature liveborn infants are also connected with stillbirths[7a]. At the present time, the number of underdeveloped stillborn infants is about the same as the number of liveborn infants dying of prematurity within the first month[57a,85]. Anticipated results of preventive measures directed toward reducing the incidence of prematurity conceivably could be masked by greater numbers of living underdeveloped infants, otherwise stillborn. The limitations imposed by available data restrict this review primarily to liveborn infants.

A premature infant is underdeveloped at birth in one or more vital systems, compared with newborn infants in general. A direct method of measurement is clearly the most useful in an endeavor to identify prematurity and to recognize the variety of developmental states manifested by infants at birth. Such a method would desirably measure function rather than form in seeking to determine whether or not an infant is fully matured. No such method exists. Techniques are known for appraising the functional maturity of the respiratory[69], renal[9,55,70], gastrointestinal[59], endocrine[43], metabolic[27,37,51,91] and hematopoietic systems[12]. For other important systems, such as cardiovascular and central nervous, only the simplest of clinical methods are

available. At best, the difficulty lies in the need to examine individually a formidable number of separate anatomical and physiological systems. General clinical use is excluded by their very number, to say nothing of technical intricacies, cost, limited availability, and often a lack of satisfactory standards. The alternative procedure is one or other of several easily performed measurements depending on the reasonable assumption that development at birth and neonatal survival are closely associated.

The two principal indices of prematurity are weight at birth and length of gestation. Birth weight is the more common. A live-born infant with an initial weight of 2500 gm. or less was suggested originally by Ylppö[97] as the mark of prematurity. This standard is currently recognized by the American Academy of Pediatrics[2] and the World Health Organization[94]. Provision is made for substituing length of gestation or clinical impression in those instances where birth weight is not known. The second measurement, length of gestation, classifies as premature those live-born infants with a gestation period of 28 through 37 weeks. This is a standard adopted in common by the United States Bureau of the Census, the Children's Bureau of the United States Federal Security Agency and the American Public Health Association[15]. Both criteria have shortcomings.

A greater exactness in method of measurement is the principal advantage of weight at birth over determination of length of gestation. The procedure of weighing is subject to little error, but what is weighed is another matter. Gross addition of diapers, blankets or a hemostat disturb the interpretation of what the baby weighs. Bias of the attendant for or against rating the infant premature sometimes acts. A technical disadvantage for epidemiological purposes in using the prescribed definition of birth weight is the lack of an established lower limit.

Length of gestation is defined[32] as extending from the first day of the last menstrual period to day of delivery. The evidence is subjective, through clinical history, depending upon statement of the pregnant woman concerned. When information is obtained during the antenatal period, the data accumulated for comprehensive numbers of pregnant women have a value in close agreement with that from smaller groups where information depends on definite knowledge of recorded basal temperature determinations[84]. Data derived from birth certificates, because in most instances they represent information obtained after the birth of the child, are often grossly inaccurate[86]. Frailties of human memory and bias arising from knowledge of birth weight are two reasonable explanations.

Both length of gestation, as determined from antenatal records, and weight at birth approximate normal frequency distributions. Each shows a slight skew to the side of smaller measurements. The appreciable biologic variability of birth weight (Table 1) depends in part on material differences in infant fat and water content at birth. Length of gestation has less variability (Table 2).

Fig. 1 demonstrates that both length of gestation and birth weight[57a] are closely associated with neonatal survival of premature infants. The difference between the neonatal mortality rates of the youngest and lightest and the oldest and heaviest is extreme. The need to recognize different degrees of underdevelopment and to effect a proper classification would seem an essential part of a search for cause and an evaluation of the problem[2,38]. A simple label

TABLE 1.—WEIGHT OF LIVE-BORN INFANTS BY RACE AND SEX

Ref. No.	*Year*	*Place*	*Race*	*Number Births*	*Mean Birth Wt. (gm.)*	*Standard Deviation*	*Coefficient Variation*
3b	1943	Cincinnati	White Male	1,731	3349	694	17.7
			White Female	1,658	2334	541	16.8
			Negro Male	1,144	3154	541	17.2
			Negro Female	1,153	3053	539	17.7
56	1951	Framingham, Massachusetts	Male	4,220	3370	572	17.0
			Female	3,909	3260	450	13.8
86	1951	Baltimore	Mixed	9,523	3204	579	18.0
76	1950	Washington, D. C.	Negro Male	5,466	3378*	400*	11.7*
			Negro Female	5,226	3269*	431*	13.2*
57b	1951	Birmingham, England	White	21,940	3390	545	16.0
74	1951	Union of South Africa	European	1,757	3390	518	15.3
			Colored	3,866	3120	518	16.6
			Bantu	7,611	3070	509	16.6
			Indian	1,738	2930	522	17.8
47	1948	West China	Chinese	3,550	3038*		
48	1930	Peking	Chinese	1,437	3052*		
89	1940	Hong Kong	Cantonese	5,437	3010*	390*	12.9*

* Full term only.

TABLE 2.—LENGTH OF HUMAN GESTATION (LIVE BIRTHS) BY RACE AND PLACE

Ref. No.	*Year*	*Place*	*Race*	*Number Births*	*Mean Duration (Days)*	*Standard Deviation*	*Coefficient Variation*
36a	1950	England	White	16,664	281	15	5.4
45	1947	England	White	3,275	278	16	5.9
3b	1943	Cincinnati	White	2,948	280	21	7.2
		"	Negro	1,895	274	21	7.7
86	1951	Baltimore	Private White	243	281	15	5.3
		"	Clinic White	419	279	18	6.5
		"	Clinic Negro	200	269	24	8.9

of prematurity does not give enough information.

Infant length at birth is a third index of prematurity. Its main usefulness is in measuring skeletal development. The measurements are not technically easy. Accurate determinations[23] are as closely related to neonatal survival as are birth weight or duration of gestation. For present purposes, birth length has no special advantage.

Numerous observations have been made on the radiologic appearance of centers of ossification[21] in the newborn, and on circumference of the head and thorax[32,34]. These measurements are mainly used in studies of growth and development, with little attempt to relate them to infant survival.

Many observations have been made on birth weight, and relatively few on length of gestation. In turning now to those generalizations possible through considering prematurity as a phenomenon of populations, the basis of study is live-born infants weighing 2500 gm. or less at birth. The condition is referred to as low birth weight. The

choice of material is again a matter of expediency. These are the data available.

Sound evaluation of the natural history of prematurity furthermore requires that instances resulting from artificial intervention be separated from those due to natural forces. The distinction is rarely made in collected series from representative populations. The usual indications for interference are disease of the mother, such as toxemia or hemorrhage, with attention to the risks experiences by both mother and fetus. In medical circles where artificial induction of labor is widely practiced for normal mothers, essentially at term, occasional delivery of infants of low birth weight may be expected through miscalculation of the duration of pregnancy. The frequency of elective intervention for general populations and the number of premature infants produced accidentally are not a matter of record. Few instances of extreme low birth weight would be expected.

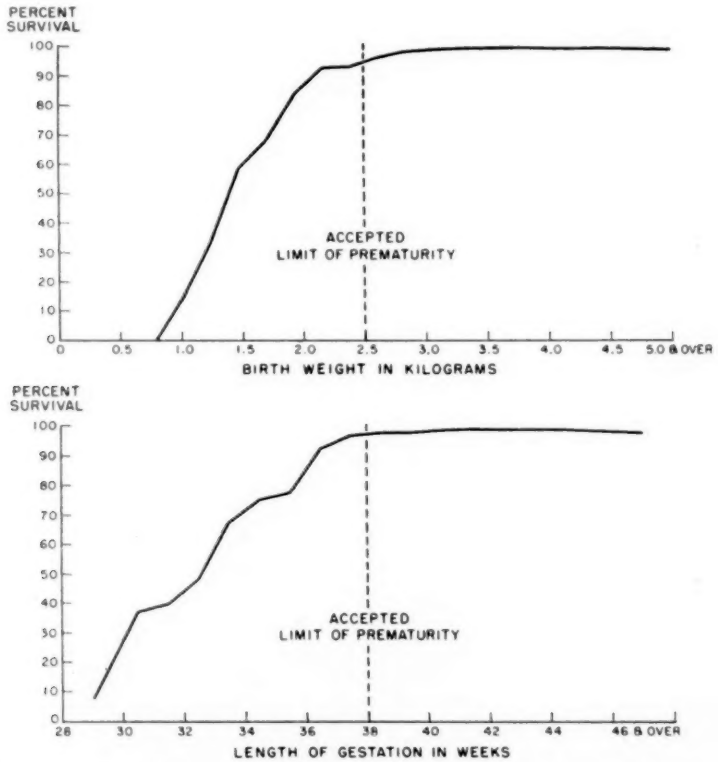

FIG. 1.—Birth Weight, Length of Gestation and Neonatal Survival, Birmingham, England, 1947[57a].

DEATHS, DEFECT AND DISABILITY. The influence of prematurity on the constitution of populations is worldwide. The relative importance of prematurity as a cause of death increases as the control of communicable diseases improves. In the decade 1939 to 1948, and for the United States, reported infant deaths from prematurity[20]

accounted for 25% of all fatalities in the pediatric age group under 15 years, comprised 50% of deaths within the first month of life, and fell among the 10 leading causes of death for the total population. Comparison of 1948 with 1939 shows a substantial decrease (24%) in the gross neonatal mortality rate, but prematurity maintained its dominant position (Table 3).

TABLE 3.—NEONATAL MORTALITY RATES, UNITED STATES

	Deaths within first month per 1000 Live Births	
Causes of Death	*1939*	*1948*
All causes	29 3	22 2
Premature birth	13 8	10 8
Injury at birth	4 4	3 4
Congenital malformations	3 2	2 9
Asphyxia and atelectasis	1 3	1 4
Pneumonia and influenza	1 2	0 8
Other specified causes	3 9	2 3
Ill-defined and unknown	1 5	0 6

SOURCE: Children's Bureau Statistical Series No. 6, Federal Security Agency, Washington, D. C., 1950.

An absolute reduction of 22% in reported deaths from prematurity occurred during this 10-year period. How much of this favorable result was due to fewer cases and how much to a lesser case fatality is uncertain. A change in classification of reported deaths is a further consideration. The Fifth Revision of the International Lists of Diseases and Causes of Death[42a], effective from 1939 through 1948, classed premature birth separately as a primary cause, with priority over other diseases of early infancy except birth injury. The Sixth Revision[42b], effective in 1949, changed the term premature birth to immaturity and made that condition a secondary axis of classification. Study of a 10% sample of 1949 to 1950 death certificates designed to test the effect of these innovations showed[63b] that immaturity unqualified, Rubric 776 under the Sixth Revision, included only 62% of deaths that would have been classified as premature birth according to Rubric 159 of the Fifth Revision. Some 22% of the total were included under postnatal asphyxia and atelectasis; 2% under pneumonia; 4% under other specified diseases of early infancy; 7% under ill-defined diseases of early infancy; and 3% under immaturity with mention of subsidiary conditions. Evaluation of secular trends for deaths attributed to prematurity necessarily takes this changed convention into account.

Infants of any appreciable degree of prematurity are disabled in varying amount and for irregular periods subsequent to birth. Disability is here understood to be temporary human incapacity without residual structural or functional impairment, in contrast to defect which involves permanent bodily change. A crude estimate of disability is to be had in the amount of medical care received, and this in turn by length of stay in hospital. Little detailed information is available. Recent experience in Illinois[65] shows an average hospital stay of 18 days for 900 live-born premature infants. The longest stay was 122 days. Such data are subject to error as an estimate of disability. Presumably infants are included who are discharged from one hospital for subsequent care elsewhere, those who die and others who remain for prolonged periods for reasons unassociated with prematurity. A more meaningful approximation would result from total length of institutional stay for non-defective premature infants before discharge to family environment, but such data are not known[90].

The community problem of prematurity is more than of death and disability. Prematurity and retrolental fibroplasia are directly related[54], a matter of no small consequence since retrolental fibroplasia is today the major cause of blindness among children in the United

States. Furthermore, the ratio of cerebral palsy[53], mental defect without cerebral palsy[52], and congenital malformations[32] among premature infants is materially greater than for the newborn child in general.

The long term prognosis of premature infants is commonly accepted[61,83] as good for those who survive the first year without inherited or acquired defect. The outcome in respect to specific degrees of prematurity is largely unknown. Studies to this end are in progress in the United States[41] and Great Britain[44]. This information is sorely needed. Too much of the existing hopeful attitude has been based on the most favorable material. Unless all living infants are considered, biologic reality is ignored.

Child Health Services[24], conducted jointly by the American Academy of Pediatrics, the United States Public Health Service and the United States Children's Bureau. This ratio is in extremely close agreement with the 6.4% obtained in a nationwide survey in Great Britain[44] during 1946. About two-thirds of live-born infants of 2500 gm. or less are in the weight group 2000 to 2500 gm.[6,22,58,86]. Collected data from various sources in the United States and from other countries are listed in Table 4. The varying rates for localities listed may be explained partly by differences in the time when data were collected, to a greater extent by differences in social and economic conditions in the several regions, and by bias arising from sampling methods.

TABLE 4. PREMATURE BIRTHS (LIVE BIRTHS 2500 GRAMS OR LESS) FOR SELECTED AREAS

			Live Births	
Ref. No.	*Place*	*Time*	*Number Births*	*Percent—2500 Gm. or Less*
6	United States	1945–47	308,487	6.1
10	New York City	1946	..	8.3
14	Chicago	1951	..	8.2
86	Baltimore	1949	9,523	8.9
44	Great Britain	1946	13,295	6.4
25	Birmingham, England	1943–46	83,118	6.0
28	Edinburgh, Scotland	1939–40	4,886	9.1
49	Paris, France	1945–47	90,000	7.2
66	Finland	1939–44	294,122	6.0

Low Birth Weight by Place and Time. An initial approach in study of any mass disease is to search for observed differences in disease distributions as they occur in various places and at different times. A comprehensive and perhaps the most reliable of estimates on the frequency of low birth weight among total live births for the United States is 6.1%[6]. The information arose from the 1945 to 1947 Study of

No good data exist for study of secular trends in low birth weight. The information available is either based on selected and changing hospital populations, is inconsistent in excluding or including multiple births and stillbirths, or rarely gives a distribution of weights within the total group of 2500 gm. and under. A universal shortcoming rests in the unknown variability associated with judgment of life at birth. Weight

at birth is now reported in most of the United States, giving promise of comparable future data over extended periods of time from which to compute informative incidence rates. Scattered data[3a,26,8,68] suggest that season has no influence on low birth weight.

Causality of Low Birth Weight. A primary objective of medical science is to identify and evaluate the multiple interactions between man and environment that result in disease. Whatever measure of success follows introduction of preventive measures lies chiefly in man's ability to make purposeful changes in himself, or in his environment, so that harmful interactions may be avoided or modified early in their course.

Knowledge of the time when causal factors operate is necessary for preventive or effective control of low birth weight. As a consequence causal influences are separated to advantage into those recognizable before conception, and those first detected during gestation. Factors operative before conception are parental and environmental; those of pregnancy are fetal, placental, maternal and environmental. This separation is for convenience of analysis. The fundamental consideration is not to lose sight of the close biologic union between fetus, placenta and mother during pregnancy.

Parental Influences Antedating Conception. Many characteristics of the mother, sometimes established long before conception and even in her own childhood, are found related to the birth weight of her infant. Age is one factor. Until about 35 years, the babies born tend to be heavier and heavier as the age of the mother increases[31]; the process then reverses, but not greatly. Birth weight also increases with parity, at least through the third birth rank. The two factors are inevitably associated. Parity appears the more important, since no consistent relationship between maternal age and birth weight of the child is evident when the factor of parity is fixed[57b]. Further evidence suggests that infants of low birth weight are more often born to mothers with history of previous low birth deliveries[3a]; and that an optimum interval between pregnancies lies between 2 and 6 years, under which circumstance low birth weight is least likely to occur[31].

Although small mothers tend to produce small babies, the correlation between maternal weight[3a], or height[7b], and birth weight, or length[17] is not great. Such factors are not to be ignored, however, in attempts to clarify interrelationships of birth weight, race and neonatal survival. Abundant evidence shows that infants of different races have different birth weights (Table 1). The relationship between birth weight and length of gestation also differs with race[3b]; Negro infants weighing 2350 gm. correspond to white infants weighing 2500 gm. There is no evidence that this is a genetic characteristic; rather there is suggestion[76] that under equal socio-economic conditions the differences tend to disappear. Further exploration of race, maternal weight and height, weight and length of infants and the question of survival seems a particularly appropriate area for research on an international scale.

Chronic maternal disease existing before conception, such as syphilis, tuberculosis, diabetes, rheumatic heart disease, nephritis and abnormalities of the genital tract, is often clinically associated with delivery of infants of low birth weight[13a,13e], but with the exception of syphilis[13b], quantitative evidence is lacking. Precise evaluation is made difficult by the frequent practice of inducing labor or performing Caesarian section under such circumstances. The effect of these diseases on the total

problem of low birth weight is presumably small and in the United States progressively decreasing.

Other parental factors preceding conception are wholly an open question. During World War II in Helsinki[71], the psychological state of mothers was advanced in explanation of fewer newborn infants of low birth weight. A careful evaluation of common factors associated with prematurity gave no adequate explanation of the observed fact of fewer underweight infants. By a process of elimination the answer was centered on the healthier psychological state of mothers brought out by the rigors of war. No direct evidence was introduced to support that speculation. Other contributions on a possible role of the maternal psyche are not known.

Similarly, reference to paternal factors is rare, even for such simple matters of age, weight, height and disease. Yerushalmy[96] reported an excess of infants with low birth weight among children of younger fathers in the United States during 1931 to 1935, an observation that remains unsupported by further evidence. No attempts to study familial factors, such as birth weights of parents and grandparents, are known.

Environmental Influence Before Conception. Most investigations of the social environment in relation to low birth weight have been limited to study of one or two variables, with other presumably important factors still to be explored. What is of more consequence, the interrelationship of factors is not always considered, rarely indeed to the point of multifactorial analysis. Such studies as have been made, of which the 1946 Maternity Survey in Great Britain[44] was the most comprehensive, have served to demonstrate that low birth weight becomes increasingly more frequent with poorer social class[31,60], is correlated with poor housing[36b], and tends toward greater frequency among married than unmarried mothers[44]. No satisfactory explanation of these findings is presently possible, although nutrition, rest and medical care during pregnancy have all been implicated.

Fetal Influences During Pregnancy. Sex affects birth weight, males being about 1.5% heavier than females of the same gestational age[3b]. In most large series, sex distribution is so nearly equal that this slight weight differential is unimportant in judging results for the group as a whole. Females have higher neonatal survival rates than males of similar weight[11], weight itself being apparently a poor criterion for comparing development between sexes.

Major congenital defects were found in some 5% of infants of low birth weight, compared with 2% for those weighing more than 2500 gm.[32]. Later the problem was approached reciprocally through studying children with anomalies. More premature births were found than would be expected[93]. Malformations influence the birth weight-survival relationship in two ways. As a result of abnormal presence or absence of tissue or fluid, many malformations directly affect weight; and it is obvious that most anomalies represent local retarded or distorted development which, in a critical location, can affect adversely extra-uterine survival.

Multiple births are a common cause of low birth weight, about 15% of infants 2500 gm. and under being twins, triplets, or quadruplets[4,7a]. However, the weight-survival relationship is also altered. For a given birth weight, twins have longer gestational periods and higher survival rates than single infants[82]. Some studies exclude multiple births; others include them, and often without differentiation from single births. Their separate consideration is

essential to proper evaluation of suspected causal factors of prematurity.

Erythroblastosis fetalis occurs in only about 0.5% of live births, and yet has been reported[77c] as the primary cause of neonatal death in as many as 10% of autopsied infants of low birth weight. The disease provides an interesting example of early induction of labor practiced because of hazard to the infant; and later recognition that the dangers of low birth weight were greater than the risk of waiting. Data on the natural effect of erythroblastosis in determining low birth weight are not at hand, but seemingly it is a minor consideration in the absence of medical interference. Since one of the cardinal signs of severe erythroblastosis is edema, weight probably over-estimates development.

Placental Influence During Pregnancy. The long neglect of the placenta as a factor in development of the fetus is just being remedied[39]. Brown, Lyon and Anderson[13d] have shown that uterine bleeding, presumably of placental origin, is associated with an increased frequency of low birth weight. A control group of 4006 mothers with no abnormality during pregnancy had an incidence of 5% of live-born infants weighing 2500 gm. or less; 399 mothers whose only abnormality was mild uterine bleeding early in pregnancy had an incidence of 14%. Of 146 mothers with placenta previa, 25% were delivered of infants under 2500 gm., and 62 with premature separation of the placenta had 50%. Artificial induction of labor or Caesarian section was performed in 2% of mothers with uterine bleeding.

Oral administration of diethylstilbestrol in increasing doses during pregnancy has been advanced as a means to reduce the frequency and degree of low birth weight[79]. The subject is currently under active investigation in a number of clinics. Stilbestrol is thought to influence the reciprocal relationship between vascularity and hormonal output of the placenta[78]. The incidence of live-born infants weighing 2500 gm. or less was 6.1% in a control group of 555 primiparous mothers, and 2.8% in a group of 387 treated with stilbestrol[80b]. In a larger but less well controlled study[80a] the weight-specific fatality rates were lower for infants of treated than untreated mothers.

Maternal Influences During Pregnancy. The evidence that such maternal factors as acute infections, trauma and intercourse act in causal relation to low birth weight is mainly based on clinical experience, not statistically verified. Toxemias of pregnancy[30] and maternal nutrition[88] have had more attention, and the facts that are known, while not conclusive, do establish these conditions in causal relation to prematurity.

Clinical experience demonstrates without doubt that toxemias of pregnancy act in causation of prematurity, but to what extent is another matter. Some reports are of 5%[4] of mothers of premature infants having that condition. Other clinics found a ratio of 25%. Somewhat less than 20% would seem a good average[3a,7a]. Varying diagnostic criteria limit comparison of experience as reported from different places. Two features have been so uniformly observed that they may be considered as established; first, that toxemia is related to parity, being more frequent in first pregnancies[30,92]; and second, that the more severe the condition, the greater the incidence of low birth weight[13c]. The frequency of infants of low birth weight among 4006 mothers having no abnormality during pregnancy was compared with that for 965 women whose only abnormality during pregnancy was toxemia. For the normal mothers, infants weighing 2500 gm. or less occurred in proportion of 5%; for those with albuminuria or hypertension above 140/90, the ratio was 7%; for

those with both albuminuria and hypertension, sometimes accompanied by other symptoms, it was 17% and for the eclamptic group, 38%. The frequency of induction of labor was also greater with increasing severity of toxemia and probably accounted in part for the greater number of infants of low birth weight.

Prenatal care including adequate protein intake, limited salt intake if preeclampsia is present, and provision for adequate rest, have greatly reduced[30] the severer manifestations of toxemia. The result is not because of any better understanding of the basic causes of toxemia of pregnancy. Whether mild toxemia is becoming any less frequent is just as uncertain.

The role of maternal nutrition in low birth weight was recently reviewed for the National Research Council[88]. Many studies[16a,33] have suggested that improved maternal food intake exerts a favorable influence on both toxemia[8,16b,92] and the birth of infants weighing 2500 gm. or less[18,19,67], but so many other factors are also involved that evaluation is uncertain. A recent study[81] suggests that the favorable effect on low birth weight so often attributed directly to nutrition is better explained by the beneficial effect of good nutrition on toxemia. The study fails to demonstrate any relationship between nutrition and frequency of low birth weight for mothers free of recognized causes. The relative importance of nutrition in the years preceding pregnancy and during pregnancy itself is not established quantitatively, but it is known[46] that in times of severe undernourishment[5], amenorrhea and infertility are common and birth weight usually lowered[77a,b].

Environmental Influence During Pregnancy. Prenatal care and maternal occupation are the principal social factors studied in relation to occurrence of low birth weight. No satisfactory measure of the quality of prenatal care has been devised. Using as simple an index as attendance at prenatal clinics[3a,31], fewer premature births were seen the greater the number of visits. Birth of infants weighing 2500 gm. or less was more frequent for working than for non-working mothers; for mothers who work outside the home late in pregnancy than for those who do not; and for mothers without domestic help than for those who had assistance in the home[31]. Other social factors are presumably interrelated with prenatal care and occupation in their effect upon mother and fetus, but have yet to be identified and measured.

Present Status of Prematurity. The past 50 years have seen outstanding improvements in the management of premature infants. The mass gains in terms of the United States population are seen in a reduction of all pertinent demographic rates. The specific premature infant mortality rates, representing deaths in the first year of life reported due to premature birth per 1,000 live births, have declined progressively[63a] from 19.4 in 1920 to 16.7 in 1930, 13.7 in 1940 to 11.1 in 1948, the current year of available data. Almost all deaths are in the neonatal period, the first month of life. The annual rates for all infant deaths per 1,000 live births were 99.9 in 1915, 64.0 in 1930, and 32.0 for 1948. Improved conditions in prematurity thus follow the same trend as infant deaths from all causes, although less decisively.

Much of accomplishment in an improved record for deaths of premature infants has been due to better medical care by practitioners, with constructive leadership by specialists in pediatrics and obstetrics strongly evidenced. Increasing numbers of infants have the advantage of birth in hospital, 13 states reporting 98% or more of such births. An important contribution has been the growing recognition of preventive

measures as an integral part of medical practice, with emphasis nowhere greater than in relation to mothers and children.

Preventive measures as a part of clinical practice had reinforcement at a somewhat later date through an evolving public health. The original primary concern with communicable diseases acted indirectly in limiting important antecedents of prematurity, notably syphilis. As communicable disease was brought under adequate control and public health broadened its activities, the field of child and maternal care was one of the first to attract early and forceful effort; and more or less the world over. The principles of prenatal and well baby care, a clinical development, were put into practice on a community basis through establishment of appropriate clinics, this being an important and direct contribution. The current extension of public health interests to such conditions as heart disease, diabetes and many other conditions expectedly will have an added indirect influence.

To what extent natural forces have acted toward a lesser frequency of prematurity is not so easily determined. Assuredly, an improved nutrition, a higher standard of living, and the many changes in physical and social environment through developing technologies and altered custom and habit, are material influences. The point is no academic matter, for an epidemiologic objective is to identify significant naturally acting influences, encourage those which are helpful and attempt to modify adverse forces to innocuousness. After all, malaria disappeared from Massachusetts and from many other parts of the United States largely because of changes incident to an advancing agriculture and industry, and with none too great contribution from medicine and public health.

An existing difficulty in analyzing causes and hence in developing means to control prematurity, is that the progress so clearly related to clinical specialization also has tended to separate into compartments the pediatrician with his concern for infants and the school children they later become, the obstetrician who supervises a series of pregnancies, and the pathologist studying placentas and the dead, yet not seeing or knowing the survivors. Public health specialists, with their efforts directed primarily toward preventing rather than curing disease, are too much a fourth distinct group. This separation of interests has led to much better data on individual features of prematurity, but the challenge is for all interested workers to reconstruct bits of people into a population and correlate significant events that affect the lives of all mothers and their progeny.

Now that better data are available, an epidemiologic approach to problems of prematurity is suggestively more useful and better indicated. Frequencies and incidence figures, time and space distributions cannot be determined until a condition is recorded, even as automobile accidents and typhoid fever in police and health department practice. The requirements for these simpler procedures are now being met in the United States through inclusion of the information in the official reports of births. The existing limitation is in reliability of the reported facts. Numerous other countries have similar systems, although for the world as a whole, serious deficiencies continue.

The more specialized and complex information essential to a study of causality in its mass relationships is now within promise of practical realization. Many hospitals keep good records; some few have most of the data needed for a study of cause. Interest

has quickened in acquiring facts that lie outside routine effort. A uniformity of definition and content of basic information tends to spread. The record in study of prematurity as a mass phenomenon, as a problem of populations, lacks much in tangible accomplishment. Many reports present informatively the experience of particular hospitals or other selected clientele. The sources are neither sufficiently numerous nor representative of social and biological differences among people to give adequate idea of the variations in origin and behavior experienced by prematurity from place to place and from time to time or to permit that generalization that defines the natural history of a physiological or a pathological state.

The search for cause is believed facilitated by viewing prematurity biologically, as something more than just another feature of a larger population problem. Prematurity is an intimate part of a reproductive wastage, and desirably takes into account antenatal deaths of other premature products of conception, which is a goodly part of stillbirths, as well as infants born alive prematurely. The field of interest might extend with profit to include abortions and miscarriages. The causes of origin may indeed be materially different, but a relation to those of prematurity is not excluded and could permit useful inferences. A practical use of such inclusive data for a population is in trial of suggested preventive measures. Presuming that a means for preventing toxemia were effective, accomplishment in respect to prematurity could well be hidden where the number of premature births remained the same but numbers of stillbirths declined.

Identification and Classification. Whether the interest be clinical or epidemiological, the first essential of investigation is to limit the field of study and to assure a reliable method for recognizing the unit of observation. Specifically applied to the study of prematurity, the point of departure is identification of that condition to the exclusion of others. A difficulty that promptly presents is that the condition is not a disease but a period of life.

The critical question is, what is prematurity? In many respects there is analogy with, what is old age? Prematurity in simplest terms is physiologic underdevelopment, compared with the average development evidenced by newborn infants. The matter is palpably more than of low birth weight. An infant may be born 7 months physiologically immature and weighing 2500 gm. On the other hand, an infant born at 9 months may weigh 2500 gm. and be a normal small baby. A practical need in the search for cause is a reliable measure of immaturity, a means by which to evaluate physiologic underdevelopment. Various possibilities have had earlier attention.

Prematurity is an abnormal event. Conceivably an infant is born underdeveloped either because of being expelled from the uterus before the usual expectancy, because development in utero was slower than usual, or because of both factors. As a matter of fact, only some 50% of live-born infants weighing 2500 gm. or less are born before expected term. Length of gestation provides a simple and reliable measure of age at birth. Many data are at hand through official report or through more precise collection, and yet for lack of analysis many elements associated with early labor remain unidentified.

Clinical and laboratory studies provide increasing information on factors controlling onset of labor, although knowledge is still indefinite[62]. Uterine distention, increased ionized calcium in blood plasma and changes in produc-

tion of sex steroids and posterior pituitary hormones help explain the phenomenon; but no specific agent has been found, if indeed one exists. Reynolds[72] suggests with reason that onset of labor is the result of gradual accelerating cooperation of many maternal, placental and fetal factors, which at a time characteristic of the species are so associated as to lead tc evacuation of the uterus. Such a species-determined characteristic is consistent with the observation that despite close correlation of birth weight and gestation, recognized factors that affect weight, such as maternal age, parity[36a] and infant sex[3b] have no influence in determining duration of gestation. Certain other factors such as race[3b], multiple births[82] and stilbestrol prophylaxis[80b], affect weight more than gestation.

The combined use of weight and age is more precise in predicting survival of the newborn infant than either alone[23,82]. The promise of this combined procedure is the ability to separate within the specific group of infants defined by an arbitrary weight standard, small babies who have had sufficient time for normal development, those larger babies who have presumably developed more rapidly than usual, and the truly immature. A working classification based on this dual standard of measurement might well include 16 classes arising from 4 divisions of weight and 4 monthly intervals. Meanwhile, the birth weight remains a practical, tested method for coping with the usual clinical problems of the newborn; and with all its shortcomings a useful source of epidemiologic data for the simple purposes of determining frequency, and time and place distributions of premature infants.

PREMATURITY OF RECOGNIZED ORIGIN. Five principal conditions, representative of the maternal-placental-fetal complex that lies in pregnancy, are commonly associated with low birth weight. The justification is based on experience and evidence. The 5 categories are multiple births, congenital malformations, toxemia, utero-placental bleeding, and a collection of maternal impairments that include syphilis, diabetes, tuberculosis, heart disease, renal disease, trauma and gynecologic abnormalities.

The frequency with which low birth weight is associated with one or more of these 5 groups is not known for general populations. Illustrative of extremes and based on the selected populations of hospitals, Cincinnati[3a] in 1941 reports that 81% of 231 live-born infants judged premature by weight, were represented in one or more of the associations mentioned; and data from the Aberdeen Maternity Home in 1945[7a] implicate one or more in about 50% of 798 live born premature infants. The categories recognized represent a curious collection of "causes", for each grouping is in itself composed of clinical conditions which, like the one they help explain, have multiple different causes. Like most problems of mass disease, the genesis of prematurity is believed to be best explained by a concept of multiple causation. Nevertheless, permutations of two or more of the items mentioned tend to occur with such frequency as to suggest an interrelationship if not a common origin, as toxemia and bleeding. The broad implication to be derived is that prematurity is an abnormal event much more commonly related to the health of the mother than to the fetus. With the exception of multiple birth, the contribution of the conceptus is less obvious.

A second shortcoming of the applied system of causality in prematurity is the inclusion of events of much question as to whether they represent cause or effect, along with others reasonably interpreted as resting in the complex of contributing antecedents. With no wish to discount the pragmatic usefulness of

this classification for clinical purposes, the intent is to draw attention to such items as the congenital anomalies. In addition to a causal relationship one to the other, both may well follow a single recognizable cause, syphilis to mention one.

A practical procedure in a search for cause would be to separate premature births according to recognized associations with multiple births, congenital malformations, toxemia, placental bleeding and other concurrent maternal disease; to determine degrees of prematurity; and to seek separate causal factors for these independent groupings. Further study of the several groups would extend to such other recognized factors as parity, placental abnormalities, interval between pregnancies, nutrition and social factors. Concomitant observations would include to advantage consideration of premature stillbirths according to the same pattern. The ideal end would be identification of a common factor or factors present in all divisions of the material not resident in allied situations, and comparable to the presence of hemolytic streptococcus in scarlet fever, erysipelas, rheumatic fever and other clinical variants of an epidemiologic unit.

Unrecognized Causes. In a significant proportion of infants of low birth weight no recognizable cause is discernible in the antecedent environment represented by the mother or evidenced by the infant itself. The group presumably increases in relative importance in the United States as the frequency of severe toxemia, tuberculosis and syphilis declines. Study of such instances as a unit is indicated, in the endeavor to determine whether they are a different population from the others as determined by combined age-weight indices, survival rates and perhaps postnatal development. This might well lead to a further objective of re-examining the validity of present limits between normal and immature development, permitting exclusion of a body of infants in reality drawn from the lowest segment of the normal age-weight distribution, and allowing a more direct approach to presently unrecognized causes of prematurity. The plan of study would follow that already outlined. Teaching hospitals would be the most desirable source of material.

Epidemiological Approach. Answers to most of the fundamental questions of causality in prematurity are to be expected from laboratory experiment, as has been true of so much in medicine. Most of what is now currently known has come from the clinic, and contributions may be expected to continue. The increasing accuracy of data and the improved recording of information make possible the addition of field methods of epidemiological study and assessment of the problem on a population basis. Because of the nature of the field the basic data will continue to be drawn in large part from the clinic. The aim of epidemiologic study is an addition of public health techniques to those of preventive medicine as contributed by the practicing physician in further limitation of prematurity.

As in most fields, the first objective is to bring to bear an elementary epidemiology which determines frequency of occurrence of prematurity and relates the phenomenon to time, place and person. The existing system of reporting in the United States gives promise of ready accomplishment. Data on the international scale and for countries with less inclusive systems of reporting will depend in many instances on actual field survey.

A second interest, truly investigative, rests in an attempt toward better definition of prematurity. A simple project is to develop better knowledge of the age-weight relationship. Opportunity for such study theoretically is provided

by existing procedure in registration of births. The difficulty lies in a recognized inexactness of recorded information. The study need not await the slow process of general education of physicians in the values of better data. In other situations an organized voluntary effort toward completeness of information in a delimited area and over a prescribed time has had success.

A third application of epidemiologic method would be long-term field study of the late effects of prematurity. Social and biological techniques would enter pertinently. The attempt would be to measure late results of prematurity in terms of physical and mental development, comparing the reaction of those born prematurely with other fractions of the population.

A final and more pretentious project is a population study whereby studies of stillbirths, abortions, and miscarriages are correlated with studies of prematurity in populations. A particular feature would be the search for common causes active in the several situations. For example, toxemia as a factor would be studied in relation to the number of deaths that occur before and after delivery and compared with other suggestive causal factors. This is in reality an evaluation of the natural history of human reproduction. The requirement by the city of New York of report of all products of conception gives promise of basic material making such an investigation possible. The more desirable procedure is that now commonly practiced in field study of other major mass diseases; namely, long term recording of the behavior of populations with the family as the unit of observation.

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BOOK REVIEWS AND NOTICES

THE SKULL AND BRAIN ROENTGENOLOGICALLY CONSIDERED. By C. WADSWORTH SCHWARTZ, PH.D., M.D., F.A.C.R., Assistant Professor of Clinical Radiology, Columbia University College of Physicians and Surgeons, and LOIS C. COLLINS, B.S., M.D., Assistant Professor of Radiology, Columbia University College of Physicians and Surgeons. Pp. 499; 365 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $10.50.

THIS book provides a competent and thorough presentation of the Roentgen findings in pathological conditions involving the skull and brain. As seems proper in a relatively small volume, little space is devoted to technical considerations which are fully treated in other works. Sections are devoted to congenital anomalies, neoplasms and inflammatory conditions; one chapter covers the skull changes in a number of miscellaneous diseases including the reticuloses, fibrous dysplasia, blood dyscrasias, etc. Encephalography and ventriculography are not considered.

To the Reviewer, the treatment of the anomalies of the cranio-vertebral junction seems deficient. Platybasia and basilar invagination are briefly defined but the clinical importance of the anomalies which constrict the upper cervical cord and medulla is not emphasized.

The authors are experienced roentgenologists and Dr. Schwartz was formerly Director of the Neurological Institute, New York. This book will take its place among the best available smaller texts on the roentgenology of the skull. H.S.

THE BATTLE FOR MENTAL HEALTH. By JAMES CLARKE MOLONEY, M.D., Pp. 105. New York: Philosophical Library, 1952. Price, $3.50.

AN interesting book on mental health by a psychiatrist who has quite a great interest in the Cornelian Corner movement throughout the United States and abroad. He gives some statistics on mental health and throughout his book points up the importance of the early days, weeks and months in the life of the child. He stresses the importance of emotional relaxation and calm on the part of the mother and the need for proximity of child and mother during infancy and early childhood. He feels that the many cases of mental disease can be prevented by more attention being paid by the medical profession to giving the child a better start in life through conditions which promote better affectional ties between child and mother in early life. Dr. Moloney speaks convincingly and tries to document his thesis for this particular aspect of preventive medicine. O.E.

ILLEGITIMATE SONNETS. By MERRILL MOORE, M.D. Pp. 125; 6 ills. New York: Twayne Publishers, Inc., 1950. Price, $2.75.

THIS would appear to be the ninth book of sonnets by Dr. Merrill Moore, a psychiatrist, from Boston. They are spontaneous and unconventional verses on human experience. Some of them are philosophical and some of them are obviously recollections of things seen and heard in Dr. Moore's experience. They provide a light, interesting reading treat. O.E.

THE AURICULAR ARRHYTHMIAS. By MYRON PRINZMETAL, M.D., ELIOT CORDAY, M.D., ISIDOR C. BRILL, M.D., ROBERT W. OBLATH, M.D., H. E. KRUGER, M.D. and eight Associate Authors. Pp. 387; 323 ills., 22 in color. Springfield, Ill.: Charles C Thomas, 1952. Price, $16.50.

THIS splendid volume presents the results of a vast amount of research into the precise nature of the mechanical and electrical events which occur in the auricles both in health and in disease. The majority of the experiments performed were devised by previous workers whose methods of observation were too indirect and too insensitive to yield conclusive results. The authors have retraced the steps of the earlier investigators using two new instruments—the high-speed cinematograph and the cathode-ray oscillograph. The result has been a refutation of much that has gone before, and the presentation of a new concept of the auricular arrhythmias. There is, of course, no way in which the authors could provide within the pages of a book the complete view portrayed by the slow-motion moving picture, but they have come remarkably close to accomplishing this by means of serial still pictures and diagrams. The reproductions are magnificent and the numerous color plates add much to the reader's appreciation of that which is so well described in the text. The organization

of the text is such that the clinician not interested in technical details may select with ease the material which is useful to him. The chapter concerning Pharmacologic Considerations is of special interest.

The final chapter of the book marshals all of the observations and summarizes the evidence supporting a unitary concept of the auricular arrhythmias, that is, that auricular extrasystoles, tachycardia, flutter and fibrillation differ only in degree rather than in the nature of the underlying disturbance. The evidence presented for this concept is very convincing, and with this there goes a clarification of a previously confused relationship. Furthermore, the treatment of these arrhythmias, hitherto empirical, has been given a rational basis, and it is to be hoped that this will lead to further improvement in the management of patients. T. D.

TOPICS IN PHYSICAL CHEMISTRY. By W. MANSFIELD CLARK, DeLamar Professor of Physiological Chemistry, The Johns Hopkins University School of Medicine. 2nd ed. Pp. 795; numerous illustrations and tables; a supplementary text for students of medicine. Baltimore: Williams & Wilkins Co., 1952. Price, $10.00.

THE chapters on Oxidation-Reduction, on Atomic and Molecular Structure, and on Colloid Chemistry have in particular been somewhat expanded. Other topics have been re-written and somewhat shortened. A great diversity of material is considered, and although statements are thus necessarily brief, they are clearly made, and numerous references are made in the text to original sources. The student with deficient pre-medical training in chemistry will have difficulty in following the derivations of formulas, but he will enjoy the lucid descriptions and the author's style that retains a bit of personality. R. H.

DAS LEBEN. By PROF. AUGUST BIER. Pp. 212. Munich: J. F. Lehmanns Verlag, 1951. Price, DM 12.50.

AUGUST Bier was a great surgeon, teacher and scientist. A factor in his greatness was that he was also a philosopher who sought the reasons behind all phenomena. He, therefore, exercised a profound influence on the Medicine of his day. After his retirement he devoted himself to his philosophical studies and their practical application. At the age of 78 he completed the first of a proposed trilogy of philosophical writings: "Die Seele," which has now reached its 65th thousand. The second was not quite finished when he died in 1949, at 87, but has now been issued posthumously: "Das Leben." The third, for which some outline studies were made, was to have described in detail the application of his philosophy in the forest he had planted and tended for over thirty years: "Der Wald in Sauen." "Das Leben" is his exposition of the teachings of the pre-Socratic philosopher, Heraclitus, and of Hippocrates, the "greatest physician." Bier has made crystal clear his interpretation of the doctrine of Heraclitus: eternal change ("everything flows"); harmony through opposites; the *Logos;* the doctrine of the humors; the doctrine of mixtures (*krasia, eukrasia, dyskrasia*); and their application in the Medicine of Hippocrates. Most useful are his suggestions as to the order in which the Hippocratic writings should be read. Bier, a positive character, has put the imprint of himself on these teachings as he applied them to the modern practical and technical field of his profession. The style is vivid and the language singularly free of cant, so that a layman and a foreigner can read with ease, interest and profit. R. K.

GRUNDZÜGE DER VERERBUNGSLEHRE RASSENHYGIENE UND BEVÖLKERUNGSPOLITIK. By PROF. DR. H. W. SIEMENS. 13th ed. Pp. 212; 88 ills. Munich: J. F. Lehmanns Verlag, 1952. Price, DM 9.60.

THIS splendid little work on heredity, eugenics and population problems first appeared over 30 years ago and such has been its excellence that its author, Prof. Siemens, one of Holland's leading dermatologists and Head of the Department of Skin and Venereal Diseases at the University of Leiden, now presents the 13th edition. Earlier editions have been translated into Swedish, English, French, Dutch and Rumanian. This convenient pocket-sized volume, well illustrated and possessing a clear and vivid style, is recommended to all physicians who read German. R. K.

COWDRY'S PROBLEMS OF AGEING. Edited by A. I. LANSING, PH.D., Washington Univ., St. Louis. 3rd ed. Pp. 1061; 233 ills. Baltimore: Williams & Wilkins Co., 1952. Price, $15.00.

IN the 10 years that have elapsed since the 2nd edition of this work appeared, there has accumulated a tremendous literature in this field, indicative of its rapidly increasing im-

portance. The 47 contributors have produced in this revision a survey of current views, knowledge, and ignorance that will be found both useful and stimulating. One major gap in medical information is in the field of allergy: there is no allergist among the contributors and in the whole book there are only two paragraphs, both of questionable value, that deal with any manifestation of allergy in the aged. This volume should find a general welcome in the profession. R. K.

PSYCHOSURGICAL PROBLEMS. By FRED A. METTLER, M.D., PH.D., SC.D., (h.c.) Editor. From the Columbia Greystone Associates, Second Group. Pp. 357, 56 fig., 4 plates. Philadelphia: The Blakiston Company, 1952. Price, $7.00.

"PSYCHOSURGICAL Problems" represents the second report of the interdisciplinary research team known as the Columbia Greystone Associates. The present report continues the follow-up observations of those cases previously reported and continues with the results of several other less commonly employed psychosurgical procedures. While the first report was particularly aimed at studying the effects and results of topectomy, the present report includes the biologic, psychologic and psychiatric alterations associated with cortical venous ligation, thermo-coagulation, as well as transorbital lobotomy. In addition, the present study has moved into an examination of the influence of social environmental factors upon the post-operative course of psychosurgical patients.

The thirty-six contributors have recorded their various procedures and observations. These include not only a description of the entire project, the hospital setting and social evaluation, but also the surgical procedures involved, general medical, hematologic and physiologic findings. Sections on neurology, olfaction, and vestibular function are included. The psychiatric side is discussed and psychometric studies, complex mental functions, attitude evaluations, psychophysiology and psychologic investigations go along with the psychiatric studies.

There is also a section concerned with the two year follow-up on the original group of patients.

The chapter on conclusions by Dr. Mettler and Dr. Landis begins with an excellent discussion of the problems and difficulties in the methodology of understanding the vast amount of data assembled in interdisciplinary approaches. In addition, the summaries of the material, anatomic, physiologic, psychologic, and psychiatric data is brought together. A logical question as to the influence of psychosurgery is discussed from the point of view of the material offered in the book.

The findings can be generally summarized in the author's own language. "We have consistently found in both the physiologic and psychologic studies a lack of specificity between the surgery done and the changes resulting. We have emphasized this lack of consistency in results and have argued that it does not fit in with the most commonly advanced theories which purport to explain or rationalize the changes sometimes observed or only temporarily encountered following psychosurgery."

The book is recommended to those interested in the interdisciplinary methodology, those interested in psychosurgery and anyone studying the psycho-neuro-physiology resulting in these procedures. H. F.

GATTENWAHL ZU EHELICHEM GLÜCK UND ERBLICHER ERTÜCHTIGUNG. By PROF. DR. HANS F. K. GÜNTHER. 3rd ed. Pp. 180. Munich: J. F. Lehmanns Verlag, 1951. Price, DM 12.

THIS is the 3rd edition of a work that first appeared in 1940 and has now reached its 43rd thousand. Based on the premise that a major reason for the failure of marriages is the wrong choice of a marital consort, the book presents a sound and practical discussion of factors to be considered in making a proper selection: age and sex differences; social status; physical beauty; disturbing factors such as city life, infatuation, and others; people who should not marry; people whom one should not marry; eugenic considerations. The book is highly recommended to all who read German. R. K.

ETIOLOGY AND DIAGNOSIS IN THE TREATMENT OF INFERTILITY IN MEN. ROBERT S. HOTCHKISS, M.D. Professor and Chairman, Department of Urology, New York University Postgraduate Medical School. Pp. 73; 18 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $2.50.

THIS is a short and well written monograph, describing both the basic physiological principles and the specific clinical examinations and tests in the diagnosis and evaluation of male infertility. The author is a well known authority in this field, and has pre-

sented the subject in a manner designed to be interesting and understandable to practitioners handling these problems. It is hoped a similar monograph on the treatment of female infertility will be forthcoming.

K. C.

SURGERY AND THE ENDOCRINE SYSTEM. By JAMES D. HARDY, M.D., F.A.C.S., Asst. Prof. of Surgery, Univ. of Tenn. Med. College. Pp. 153; 43 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $5.00.

WRITTEN by a surgeon for surgeons, this small book represents the valiant efforts of a young and capable physician to discuss simply the pertinent facts which are available concerning the relationships between Surgery and the Endocrine System. The first section relates primarily to the physiologic responses to surgical trauma with a description of the endocrine and metabolic changes which ensue. The second section is concerned with diagnostic aids for surgically treatable endocrine disorders as well as recommended preoperative and postoperative techniques.

This book is in no sense complete and would have been more valuable if written in conjunction with an Endocrinologist. Nevertheless, it will have served its purpose amply if it succeeds in making surgeons at large more familiar with the role the Endocrine System plays in modern surgical thinking.

W. P.

INDUSTRY AND TROPICAL HEALTH: PROCEEDINGS OF THE FIRST INDUSTRIAL TROPICAL HEALTH CONFERENCE, SPONSORED BY THE HARVARD SCHOOL OF PUBLIC HEALTH. Pp. 316; 154 ills. Boston: The Harvard School of Public Health, 1951. Price, $10.00.

EXPERTS in Tropical Medicine from many parts of the world gathered in Boston in December, 1950, to tell of their experiences and exchange views on their problems. This volume records their discussions on the problems of health as met and solved by industry in the Middle East, Tropical Africa, the Far East and in Tropical America; the organization of industrial health services; antibiotics in certain tropical diseases; nutrition; the control of infectious diseases; industrial health hazards; current research. The book offers a wealth of first-hand up-to-date practical information, and at the same time gives eloquent testimony to the important role that Western enterprise, through its medical programs, is playing in World relations. The Harvard School of Public Health and especially its Dean, General James Stevens Simmons, are to be congratulated on the meeting and on this fine record of the occasion.

R. K.

LA FUNZIONE EMOBLASTICA DEL SISTEMA ISTIOCITARIO. By CARLO BIANCHI, M.D., Clinica Medica dell'Universita', Parma, Italy. Pp. 280; 39 tables with 180 microphotographs. Parma: Instituto Bioterapico Carlevaro Editore, 1951. Price, Lire 3,000 (about $4.60).

THE fundamental concept developed by the author, mostly with the aid of histopathological studies, is that the common element joining all essential hemopathies is the "Hemohistioblast" or "Histiocytes" (Ferrata). Under normal conditions all hemopoietic elements derive from this cell; faulty multiplication and/or differentiation of these cells form the basis for all primary hemopathies.

The author, after a clear and concise historical review of the essential contributions to the development of the concept of the R.E. system, establishes vital staining, or "proprietá cromo-granulopessica" (with the significance of the "Speicherung" of the German authors) as the basic differential character of the hemohistioblastic elements. In the chapter on embryology the evolution of the mesenchyme and its relationship to the R.E. system are well discussed; this is followed by a review of the functional properties of these cells. Another fundamental property attributed to the hemohistioblasts is the specific manner of reaction of the histiocytic cells to stimuli. This note of functional approach to identification of cellular elements is particularly noteworthy in view of the prevalence of morphological studies in many publications on the same subject in past years. After a thorough review of the hemopoiesis, with observations of both morphological and functional aspects, the author gives much consideration to the pathology of the histiocytic system, particularly the leukemias, which are all considered as being essentially a product of "displasia" (faulty formation) of the histiocyte.

There is a technical appendix dealing with all processes of preparation and staining of the cells. The book is well written, clearly printed and has good illustrations with excellent legends. This work constitutes an outstanding contribution to the field of hematology.

M. S.

NEW BOOKS

Doctors in Blue: The Medical History of the Union Army in the Civil War. By GEORGE WORTHINGTON ADAMS, Dean and Professor of History at Colorado College. Pp. 253; 16 ills. New York: Henry Schuman, Inc., 1952. Price, $4.00.

HISTORIANS of wars have a way of neglecting the role of disease, wounds, and the men and measures engaged in their control, as all of these affect the outcome of wars. The pages of their histories bristle with names and details concerning matters strategic, tactical and logistic, but never a mention of a doctor, a hospital, a disease. It is, therefore, refreshing to see this well-written and well-documented history of the medical activities of the Union Army. The book fills a real need in the story of American Medicine and the history of our Civil War. R. K.

The Medical Clinics of North America. Tulane University—Toronto Number, March, 1952. Pp. 300; illustrated. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00 per annum.

THE current issue includes two symposia, the first, on Symptoms under the editorship of Dr. Roscoe L. Pullen and with contributions from various members of the staff of Tulane University and the Ochsner Clinic in New Orleans; the second, on the Psychological Aspects of Medicine under the editorship of Dr. R. H. Farquharson, with a group of contributors from the University of Toronto and the Toronto General and Psychiatric Hospitals. The articles are all well done and measure up to the high standard of excellence of this fine publication. R. K.

Health, Happiness and Hormones. By MAX R. RUBINSTEIN, M.D. Pp. 223. New York: Hermitage House, 1952. Price, $3.00.

THROUGHOUT this book, the author attempts to impress the reader with the importance of the endocrine system without overemphasizing the results that may be anticipated from the use of hormonal products. In spite of his many protestations, he has fallen into the error of exaggerating the role of the hormones in "Health and Happiness." There are many misstatements in this book. He claims, for example, that growth hormone may be used in the short child "with decided success." This reviewer is not familiar with one reported instance of good results in such situations with growth hormone. Dr. Rubinstein talks about Froelich's Syndrome as though it were a very common entity, and one cannot help but wonder whether he knows how to differentiate this from simple obesity. His discussion on homosexuality is particularly disturbing to this reviewer. The author claims that the hormonal pattern in homosexuality is different from that of the normal. I would certainly like to know the origin of these data. This book is directed toward the laity and, in spite of the above and other objections, the approach is still considerably better than that of most of the articles which are being printed in popular publications. W. P.

Liver Injury: Transactions of the 10th Conference, May 21-22, 1951. Edited by F. W. HOFFBAUER, M.D., Dept. of Med., Univ. of Minn. Med. School. Pp. 320; 122 figs. and 21 tables. New York: Josiah Macy, Jr. Foundation, 1951. Price, $3.75.

THIS volume recounts in its entirety the proceedings of the tenth annual meeting of a specially selected group of investigators interested in various aspects of liver disease. The following topics were formally presented and informally discussed at this meeting: Serum Proteins and Lipids; Mechanism of Action of Lipotropic Factors in Animals and in Man; Experimental Ischemia of the Liver and Hepatic Coma; Micro-Anatomy of the Hepatic Vascular System; The Effect of Insulin on the Liver in Normal and Diabetic Man; and Liver Disease in Jamaican Children. The data and observations described in the several presentations and discussions make the recorded transactions a rich source of information. While the volume holds particular interest for those with a continuing interest in disorders affecting the liver, it should prove a valuable current reference for any who may wish to become acquainted with the latest information on these particular topics. J. B.

Recommendations of the International Commission on Radiological Protection and of the International Commission on Radiological Units, 1950. National Bureau of Standards Handbook 47. Pp. 29. Washington, D. C.: U. S. Department of Commerce, 1952. Price, $.15.

Studies on Testis and Ovary, Eggs and Sperm. Edited by EARL T. ENGLE, College of Physicians and Surgeons, Columbia University. Pp. 237; 95 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $7.50.

THIS is a collection of papers presented at the Conference sponsored by the Committee on Human Reproduction. They relate essentially to the function of the testes and the ovaries, and will be of interest to workers in the field. These articles are primarily of fundamental importance and are generally not of immediate practical value. W. P.

Metabolism and Function in Nervous Tissues. Edited by R. T. WILLIAMS. A symposium held at the London School of Hygiene and Tropical Medicine on November 10, 1951. Biochemical Society Symposia No. 8. Pp. 101. New York: Cambridge University Press American Branch, 1952. Price, $2.75.

THIS volume contains excellent presentations of research on metabolism and function in nervous tissue. Nine authorities are included. Bibliographies are extensive and excellent. A good picture of the present condition of research upon the fundamental biochemistry of brain tissue is presented. M. O.

Transactions of the Second Conference on Problems of Consciousness, March 19-20, 1951, New York. Sponsored by the Josiah Macy, Jr. Foundation. Edited by HAROLD A. ABRAMSON. Pp. 178. New York: Josiah Macy, Jr. Foundation, 1951. Price, $3.25.

Principles of Refraction. By SYLVESTER JUDD BEACH, M.D., F.A.C.S., Consultant, Staff Maine Eye and Ear Infirmary. Pp. 158; 18 ills. St. Louis; C. V. Mosby Co., 1952. Price, $4.00.

Liver Injury. Trans., 9th Conference, Apr. 27-28, 1950. Edited by F. W. HOFFBAUER, Univ. of Minn. Med. Sch. Pp. 232; 93 ills. New York: J. Macy, Jr., Found., 1951. Price, $3.00.

X-ray Protection Design. By HAROLD O. WYCKOFF and LAURISTON S. TAYLOR. Pp. 36; 7 figs.; 18 tables. Washington: Bureau of Standards Handbook 50, U. S. Department of Commerce (Government Printing Office), 1952. Price, $.15.

A concise, authoritative handbook giving detailed specifications for designing safe diagnostic and therapeutic Roentgen installations. H. S.

Rehabilitation Nursing. By ALICE B. MORRISSEY, B.S., R.N. Pp. 299; 58 ills. New York: G. P. Putnam's Sons, 1951. Price, $5.00.

Between Two Worlds. The Memoirs of a Physician. By BENJAMIN L. GORDON, M.D. Pp. 354, 1 ill. New York: Bookman Associates, 1952. Price, $4.00.

THIS is an autobiography of a physician who was born in Lithuania and who came to Philadelphia where he studied medicine. It is interesting in that it portrays the drives and achievements of a young man who had to make his own way.

The Contribution of Medicine to Our Idea of the Mind. The Rede Lecture for 1952. By SIR RUSSELL BRAIN, M.A., D.M., (OXON.), President of the Royal College of Physicians. Pp. 30. New York: Cambridge University Press American Branch, 1952. Price $.50.

Radiological Monitoring Methods and Instruments. U. S. Department of Commerce, National Bureau of Standards Handbook 51. Pp. 33; 6 ills. Washington, D. C., 1952. Price, $.15.

THIS current pamphlet in the series of radiation physics pamphlets by the National Bureau of Standards discusses radiation monitoring instruments, with specific reference to the type of instrument to be used for given radiation hazards; it maintains the authoritative standards set by the previous pamphlets of this series. R.R.

Physiological Changes in Plasma Proteins Characteristic of Human Reproduction. By ICIE G. MACY, PH.D., SC.D., Director of the Research Laboratory, Children's Fund of Michigan, and HAROLD C. MACK, M.D., Department of Obstetrics and Gynecology, Harper Hospital, Detroit. Pp. 170; 16 ills. Detroit: Children's Fund of Michigan, 1952. Free to workers in this field.

THIS volume was produced to make the results of the authors' electrophoretic studies of blood plasma proteins available in more complete form than is possible in journals.

Klinische Probleme der Vegetativen Regulation und der Neuralpathologie. By PROF. DR. FERDINAND HOFF, Director of the Medical Clinic, Univ. of Frankfurt. Pp. 43; 9 ills. Stuttgart: Georg Thieme Verlag, 1952. Price, DM 2.70.

NEW EDITIONS

Review of Pharmacy. By GEORGE W. FIERO, PHAR. D., Ph.D., 7th ed. Pp. 122. New York: John Wiley & Sons, Inc., 1952. Price, $3.25.

THIS brief book is properly entitled a "Condensed Review of Pharmacy," since it presents in tabulated form abbreviated information concerning drugs and preparations included in the official compendia. Its brevity seems to preclude the possibility of its use as a text and limit it to the purpose for which it was obviously intended—a study aid for examinations. J. S.

Office Endocrinology. By ROBERT B. GREENBLATT, M.D., Medical College of Georgia. 4th ed. Pp. 561; 276 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $10.50.

THIS is an interesting and valuable book covering the large field of general endocrinology. It is written for the general practitioner by a man who has had tremendous experience with endocrine problems. He has kept this book on a practical basis. It is well written, easily understandable and will prove to be of great diagnostic and therapeutic aid to the practicing physician.

W. P.